PROSPECTS
IN PHARMACEUTICAL SCIENCES

Prospects in Pharmaceutical Sciences, -
https://prospects.wum.edu.pl/

Review

ALPHA-LIPOIC ACID IN PHARMACEUTICAL DEVELOPMENT: A COMPREHENSIVE REVIEW OF ITS THERAPEUTIC POTENTIAL AND MOLECULAR MECHANISMS

Oruc Yunusoglu[1], Esma Koyuncu[2]
[1]Department of Pharmacology, Faculty of Medicine, Bolu Abant Izzet Baysal University, Bolu, Turkey

* Correspondence, e-mail: orucfarm@gmail.com
Received: 02.04.2025 / Accepted: 25.05.2025 / Published online: 17.08.2025

ABSTRACT

Alpha-lipoic acid (ALA), also known as thioctic acid is a lipid acid with strong biological activity synthesised from octanoic acid in prokaryotic and eukaryotic microorganisms, plants, and animals. It is gaining attention for its potential therapeutic benefits for a wide range of health problems. A comprehensive systematic literature review on ALA has been performed without temporal restrictions utilizing the PubMed, Scopus, Embase, ScienceDirect, SciELO, and SciVerse databases. Different *in vitro*, *in vivo,* and clinical studies have demonstrated numerous potent pharmacological activities of ALA, including antioxidant, anti-inflammatory, antimicrobial, anti-Alzheimer, antiepileptic, antiparkinsonian, anxiolytic, effects on schizophrenia, neuroprotective, antidiabetic, antiallergic, anticancer, anti-osteoporosis, cardioprotective, hepatoprotective, anti-obesity, anti-aging, reproductive system, and so on. Although dietary supplements (tablets, capsules, etc.) containing ALA are available due to their various biological activities, there are no Food and Drug Administration (FDA) and European Medicines Agency (EMA)-approved over-the-counter (OTC) ALA drugs in the world. Pharmacokinetically, ALA has an oral bioavailability of roughly approximately 30% due to its brief blood half-life, significant presystemic clearance, and hepatic first-pass metabolism. However, the use of different innovative formulations has greatly enhanced ALA bioavailability. The data obtained show that ALA liquid formulations have higher plasma concentrations and therefore bioavailability compared to solid dosages. These innovative approaches hold promise for the development of improved ALA-based treatments across a broad spectrum of health conditions.

KEYWORDS: Alpha-lipoic acid; Therapeutic potential; Pharmacological activities; Pharmacokinetics; Pharmaceutical development.

1. Introduction

Alfa-lipoic acid (ALA), IUPAC name: 5-(1,2-dithiolan-3-yl) pentanoic acid referred to as simply thioctic acid, is a type of eight-carbon, composed of sulfur lipid acid formed by the majority of prokaryotic and eukaryotic bacteria (Fig 1). ALA synthetase is responsible for this synthesis in both plants and mammals. Its synthetase is responsible for this synthesis in both plants and mammals [1]. Snell et al. are the initial group to extract ALA from the potato source [2]. These novel methodologies offer potential for the advancement of enhanced ALA-based therapies across a wide range of health disorders. ALA was recognized as a catalytic agent for the oxidative decarboxylation of pyruvate and α-ketoglutarate in 1951, and it has since been extensively investigated by chemists, biologists, and clinicians regarding its function in energetic metabolism and its protective effects against mitochondrial dysfunction induced by reactive oxygen species.

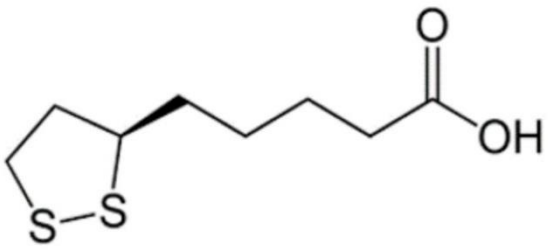

Figure 1. Chemical structure of alpha-lipoic acid.

Reed et al. re-isolated or structurally classified the components [3]. ALA has been eliminated from the list of essential vitamins since it may be synthesized by animals [3, 4] . ALA can be sourced from animals that are red, broccoli, tomatoes, potatoes, Brussels sprouts, spinach, white and brown the rice [4]. Dihydrolipoic acid (DHLA) is the decreased version, whereas ALA is the oxidized form [5]. Human serum contains about 16 mg/L of it [6]. An essential part of enzyme complexes like pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, ALA contributes significantly to the generation of energy in the mitochondria [7]. These enzyme systems, that function an important role in metabolizing carbohydrate, help to synthesize stored energy and control several metabolic processes. According to studies, ALA effectively scavenges hydroxyl radicals, singlet oxygen, and hypochlorous acid. Furthermore, it has been noted that chelation of copper, iron, manganese, and other metals is crucial in lowering oxidative stress [8–10]. (1) Quick sequestration of reactive oxygen species (ROS); (2) regeneration of endogenous antioxidants, including glutathione, vitamins E, and C; and (3) metal chelation activity, which lowers ROS formation, are the antioxidant qualities of ALA [7]. ALA's biological impacts extend beyond its antioxidant properties. The safe and successful therapy of ALA is available in many clinical settings [11, 12]. Reliable information on the therapeutic application of ALA in a variety of diseases has been supplied by the following conditions: sepsis, cancer, neurodegenerative transplantation and neuropathy, ınsulin dependency and having diabetes, regrowth of tissue, ischaemia-reperfusion damage, and ageing. It's been proved which ALA can lower oxidative stress and regulate the amount of glucose metabolism linked to insulin resistance and diabetes components [13, 14]. Autophagy is a key molecular process that facilitates the elimination of damaged or malfunctioning cellular components [15, 16]. ALA activates AMP-activated protein kinase (AMPK), promoting autophagy through ULK1 phosphorylation. It is demonstrated to alleviate various factors that cause cell damage by inhibiting autophagy through different pathways [17, 18]. Furthermore, it has been proposed that ALA may prolong brain function and postpone age-related medical decline in conjunction with its neuroprotective actions [19, 20] . However, there are no FDA and EMA-approved OTC ALA drugs worldwide. ALA has been demonstrated to boost cellular energy production, inhibit inflammatory processes, and protect against free radicals in neurodegenerative illnesses including Parkinson's and Alzheimer's [21, 22]. A summary of the biological activity of ALA is presented in Fig 2.

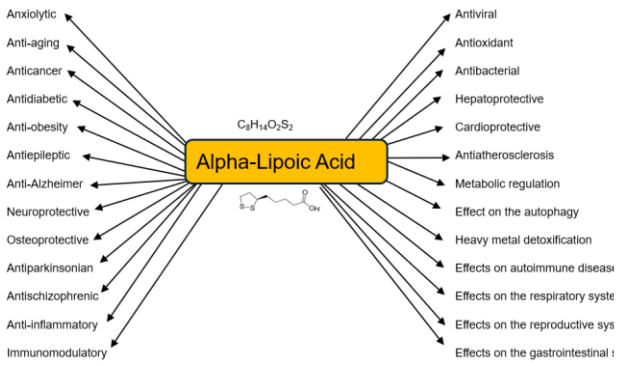

Figure 2. Summary of biological activity of alpha-lipoic acid.

According to clinical research, ALA's neuroprotective and anti-inflammatory properties may halt the progression of disease [23, 24]. In addition to its antioxidant ability, recent research has demonstrated that ALA has immunomodulatory and anti-inflammatory qualities [25]. When combined with additional anti-oxidants such as vitamin C, E, and co-enzyme Q10, ALA and its reduced derivative DHLA can strengthen the cellular defense system [26, 27]. Furthermore, ALA may be useful in lowering the difficulties associated with obesity because it has been shown to control lipid metabolism by activating the adenosine monophosphate-activated protein kinase (AMPK) pathway [21, 28]. Although certain possible adverse effects have been documented, ALA is generally regarded as safe and is also utilized as a dietary supplement [29, 30]. These consist of skin responses, nausea, and, in rare instances, hypoglycemia [31]. Excessive dosages have been shown to be detrimental and to significantly alter blood glucose levels, especially in diabetics [22]. More data on the bioavailability, suitable dose, and long-term stability of oral and intravenous ALA are needed for clinical study [7, 25, 32].

ALA possesses two distinct enantiomeric forms: S-(-)-ALA and R-(+)-ALA. R-(+)-ALA is the biologically active enantiomer, exhibiting superior bioavailability, potency, and therapeutic efficacy compared to the S enantiomer (Fig 3.). In several instances, the S-enantiomer was documented as inactive and was even demonstrated to induce mortality. Consequently, the utilization of enantioselective R-(+)-ALA in dietary supplements and pharmaceuticals is advantageous [7, 33].

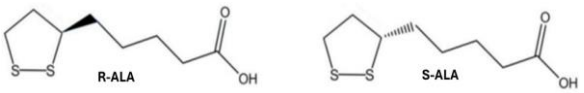

Figure 3. R and S enantiomers of alpha-lipoic acid.

2. Materials and Methods

The search for bioactive effects and clinical outcomes of ALA mentioned in this review was performed in PubMed, Scopus, Embase, ScienceDirect, SciELO, and SciVerse database, without any time interval, articles published in English language were selected.

3. Pharmacokinetic properties of alpha-lipoic acid

3.1. Absorption of ALA.

Whenever ALA is given orally or intravenously, it is absorbed from the stomach and small intestine, processed in the body, and delivered to the livers by portals circulatory as the remainder of the tissues by the circulatory system [34]. ALA is water-soluble, hydrophilic, and lipophilic, allowing it to traverse the blood-brain barrier and exist both intracellularly and extracellularly, including within mitochondria [35]. Because gastrointestinal absorption varies and decreases with food intake, ALA should be taken 30-60 minutes before a meal or at least 120 minutes afterward. ALA reaches maximal plasma levels within 30-60 minutes of intake and is thought to be processed in the liver. ALA, as a weak acid, benefits from the stomach's acidic environment for gastric absorption, reducing competition with other nutrients during intestinal absorption, hence it is

best to take ALA on an empty stomach [36, 37]. Studies conducted throughout the years have demonstrated that ALA has low solubility in watery and acidic environments such as the stomach. This reduces its oral bioavailability significantly. Furthermore, the first section of the small intestine aids in the absorption of ALA via particular transporter proteins [9, 10]. At low quantities, ALA is absorbed via active transport, which is driven by transporters and competes with short-chain fatty acids, but at high concentrations, it is absorbed via diffusion [38].

3.2. **Distribution of ALA.**

Our observations suggest that a continuous flow of [14C] ALA is quickly established via the skin. In just 30 minutes, the first stripping of the stratum corneum included 100 times more [14C] ALA than the final stripping, with intermediate strippings carrying exponentially declining levels. Sections from the papillary dermis showed nearly equal quantities of [14C]-ALA, similar to research on linoleic acid or benzoyl peroxide [39, 40] . The lipid-rich nature of sebaceous glands in this region and the mild hydrophilicity of ALA may explain its higher concentrations in the epidermis of the stratum corneum compared to the dermis and subcutaneous tissue. After permeating the skin, ALA is converted to DHLA, a more effective antioxidant (high-Performance liquid chromatography/HPLC results confirm). This study shows that ALA rapidly absorbs into mouse skin. ALA is a promising topical treatment for oxidative stress [41].

3.3. **Metabolism of ALA.**

R (+)-ALA is a naturally happening molecule of which functions as an important co-factor in particular dehydrogenase combinations. In this investigation, nine healthy volunteers received (600 mg) from racemic ALA orally numerous times every day. Plasma, which concentration-time spirals for ALA metabolites, urine excretion levels, and pharmacokinetic characteristics were investigated. The quantitative results provided here show which ALA come by considerable liver disease metabolism in its initial phase. ALA's biological transformation involves ß-oxidation for the acidic carboxylic flanking chain with S-methylation to the dithiolane molecule. Nevertheless, conjugative metabolic showed seen to not polar metabolite and the source chemical, the excretion of several metabolic products in urine did not use a significant act on ALA cleanup [42]. ALA is rapidly absorbed in the colon, structurally changed, transported to numerous organs, and then eliminated. After a week of ALA supplementation, exempt ALA was identified in several textures, with the utmost levels in the heart. In vitro studies indicate that ALA is quickly absorbed by cells and turned to DHLA. Medium-chain fatty acids (octanoate) block ALA molecules from being absorbed and excreted in the liver and bile. Low metabolite levels indicate that most of the added ALA is unaltered [38]. Early research suggests that ALA can cure metabolism of glucose and impact metabolic pathways at multiple levels. A study on rabbits found that after 15 days of ALA supplementation, plasma, liver, and aortic lipid levels decreased due to diet-induced increases [43].

3.4. **Excretion of ALA.**

Urinary excretion peaks 3–6 hours after ALA administration, proffering that lipoate metabolites are cleared out of rats faster than reported in many studies. Thereabouts 45% of radiation from ısotope classified ALA was expelled in urination within the initially twenty-four hours, while only 3% was eliminated via feces. Studies on the metabolism of ALA in both humans and rats suggest that very little of the administered dose is excreted in its unchanged form. Four hours after intraperitoneal or oral administration of DL-[14C]-ALA, the highest radioactivity levels were looked at in the liver; however, after a whole day, radioactivity was found in skeletal muscle. This aligns with in vivo studies demonstrating the liver's high capacity to take up and store these compounds [43].

3.5. **Bioavailability of ALA.**

Regardless of its many biological functions, investigations have shown that ALA has limited therapeutic value due to its pharmacokinetic profile. The data show a low halfway life and around 30% accessibility, which is because of liver disease breakdown, decreased solubility, and stomach instability [44]. ALA supplements should be taken on an empty stomach to avoid competing with other nutrients during absorption [44]. Food consumption and severe renal impairment both have an effect on ALA's pharmacokinetic characteristics [45].

4. Development in The Therapeutic Perspectives of Alpha Lipoic Acid

4.1. Antioxidant effects.

Oxidative stress plays a role in the pathology of cardiovascular diseases, cancer, diabetes, neurological disorders (such as epilepsy, Parkinson’s, Alzheimer’s and Down syndrome), psychiatric disorders (including bipolar disorder, depression, schizophrenia), aging process pulmonary diseases (including chronic obstructive pulmonary disease and lung cancer), and renal disease [46-50]. In an organosulfur compound, ALA may neutralize ROS and enhance the function for tissue antioxidant enzymes including glutathione peroxidase and superoxide dismutase [9, 10, 31, 51]. Additionally, ALA reduces oxidative stress by lowering peroxidation of lipids and enhancing antioxidant enzyme function, and regulating gene expression related to antioxidant mechanisms [21, 52] Findings in this section highlight ALA's impact on the antioxidant status in various organs. Supplements containing apocynin, ALA, and probiotics have shown positive effects on antioxidant capacity in lung tissues [53]. It has been demonstrated that ALA positively modulates energetic aspects and oxidative stress under hypoxic/reperfusion (H/R) conditions. Furthermore, ALA has been shown to be effective as a supplement against hypoxia-induced damage [54]. Antioxidants like ALA are known to trigger increased antioxidant and phase II and III responses. Pre-treatment with ALA prevented the reduction in total antioxidant capacity in the liver and the adverse effects in the brain [55]. ALA has proven effective in enhancing antioxidant capacity and delaying the browning of lychee fruit skins. This finding suggests that due to its antioxidant properties, ALA may increase the tolerance of plants to abiotic stresses [56, 57] Therefore, ALA may have a promising use in post-harvest fruit storage, encouraging its application in food chemistry [58]. ALA is a natural antioxidant used to treat diabetic polyneuropathy [31, 59]. It has also been reported that ALA exhibits extraordinary antioxidant properties not only in gastric ulcers but also in the small and large intestines by eliminating heavy metals that cause increased oxidative stress and rebuilding the antioxidant defensive

system [60–62] Combinations of ALA also show antioxidant properties. For example, a combination of erdosteine and ALA led to a reduction in oxidative stress markers, suggesting an interaction that offers protection against these oxidative processes [63]. ALA's effects on reactive sulfur species (RSS) have been shown to directly trigger antioxidant, anti-inflammatory, and cytoprotective responses [64]. The beneficial effects of CoQ10 or ALA may involve direct changes in histological structure, an increase in growth-related hormones and antioxidant gene expression, or indirect effects such as increased vitamin E levels [65]. Although the metabolic effects are not fully understood, the combination of ALA and acetyl-L-carnitine (ALC) may be beneficial as a dietary supplement for preventing oxidative stress [66]. A new synthesis strategy has been proposed for the preparation of ALA-loaded chitosan derivatives, which could potentially serve as antioxidant biomaterials in the food and biomedical industries [67]. On the other hand, other forms of ALA also exhibit antioxidant properties. For instance, both ALA and its decreased a component, DHLA, display three unique antioxidant effects. ALA and DHLA contain metal-chelating capabilities and can neutralize hazardous reactive oxygen species. Furthermore, ALA demonstrates a capacity to regenerate endogenous antioxidants, showcasing its networking abilities [68]. To study the antioxidant activity of ALA and other formulations, cell viability was observed following free radical induction using H2O2 in human fibroblasts. It is suggested that ALA could serve as a potential antioxidant delivery system in cosmetics or pharmaceuticals that do not contain artificial protective substances [69]. Finally, (R)-ALA supplementation reduces oxidative stress and damage associated with aging while improving metabolic activity indices [33]. The schematic view of the potential antioxidant pathways of ALA is presented in Fig 4.

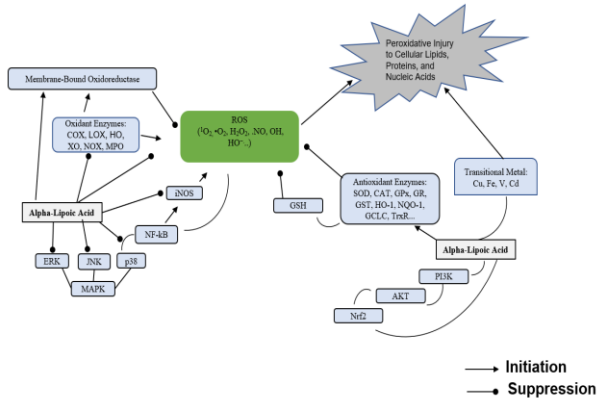

Figure 4. Schematic overview of potential antioxidant pathways of alpha-lipoic acid.

Akt: Protein Kinase B; CAT: COX: Cytochrome c Oxidase, Catalase; CLC: Glutamate Cysteine Ligase ERK: Extracellular Signal-Regulated Kinases; GSH: Reduced Glutathione; GPx: Glutathione Peroxidase; GR: Glutathione Reductase; GST: Glutathione S-Transferases; HO-1: Heme oxygenase 1; iNOS: Inducible Nitric Oxide Synthase; JNK: c-Jun N-terminal kinase. MAPK: Mitogen-Activated Protein Kinase; PI3K: phosphatidylinositol-3-kinase; MPO: Myeloperoxidase; NF-κB: Nuclear Factor kappa B; Nrf2: Nuclear Erythroid 2-related Factor 2; NOX: oxidase; NQO-1: Quinone Oxidoreductase: ROS: reactive oxygen species; XO: xanthine oxidase; SOD: superoxide dismutase, LOX: Lipoxygenase; HO: Heme oxygenase; TrxR: Thioredoxin reductase.

4.2. Anti-inflammatory effects. Abnormal biological responses to skin injuries following diseases, trauma, and surgeries inevitably lead to serious complications [70]. ALA is a safe native compound that acts a role in many physiological procedures and has a major function in immune system modulation. Diverse studies have demonstrated that ALA and DHLA are extensively involved in inflammatory processes that require the precise regulation of complex and overlapping pathways [25]. Gold nanoparticles (AuNPs), epigallocatechin gallate (EGCG), and ALA have been shown to have antioxidant effects and assist in wound healing. In one study, AuNPs led to enhanced wound healing effects [71]. When combined with hyperbaric oxygen therapy, ALA supplementation downregulated inflammatory cytokines in human subjects with non-healing wounds [72]. It is also suggested that ALA, as an antioxidant, enhances the antioxidant activity of EGCG. This finding may support]future studies on the use of other antioxidant factor in the therapy of cutaneous wounds [71]. In another study, oral ALA administration increased splenic Treg cells that act a role in combating excessive inflammation and inhibited the fabrication of vessel and intracellular adhesion particles (VCAM-1 and ICAM-1) [73–75]. In vitro and in vivo studies have shown that ALA has a modulatory effect on biochemical parameters such as myeloid differentiation factor 88, mitogen-activated protein kinases, T-tetradecanoylphorbol-13-acetate, toll-like receptor, tumor necrosis factor receptor associated factor 6 and inhibitor kappa B. Furthermore, ALA reduces the phases of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-8, IL-17, and interferon and induces the decontrol of the anti-inflammatory cytokine IL-10 [25, 74, 75]. Additionally, ALA can accelerate the process of hematoma resorption by increasing the levels of vascular endothelial growth factor and alpha glazed brawn actin, while decreasing the expression of NF-κB and MMP-9 [75, 76]. All these effects also contribute to the acceleration of tissue repair and angiogenesis [75]. The induction of endothelial adhesion molecules by inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) is dependent on the activation of the NF-κB transcription factor [77]. Understanding how ALA inhibits the NF-κB/IkB regulation system is critical for discovering new anti-inflammatory medicines that can prevent atherosclerosis and other inflammatory illnesses. These results show that ALA significantly reduces TNF-α-induced mRNA and cellular adhesion molecule synthesis of proteins, which inhibits monocyte adherence [78]. Factors that block NF-κB signaling and thereby inhibit the expression of adhesion molecules and leukocyte-endothelial interplays in vitro also show significant impacts on inflammatory answers in vivo [79, 80] Research on ALA's impact on autoimmune conditions like multiple sclerosis (MS) has also shown that it suppresses T-cell migration, which lowers inflammation in the major neurological structure. MS is characterized by abnormal control of the inflammatory response [29]. Previous research suggests that ALA reduces the producing of pro-inflammatory cytokines such IL-2, IFN-γ, and TNF-α by regulating cAMP levels [81]. These data show that cAMP may be involved in ALA's mechanism of action in secondary progressive multiple sclerosis, and that there may be a distinct answer to ALA in relapsing-remitting MS patients, which might affect the efficacy of immunomodulatory medications. Yadav et al. found that mouth ALA lowered blood matrix metalloproteinase 9 (MMP-9) levels in MS patients, which is

linked to inflammatory disease activity [23, 82]. ALA dramatically improves diabetic neurovascular and metabolic problems, and it may also have a role in cardiovascular protection and anti-inflammatory activity [83, 84]. Both in vitro and in vivo investigations have disclosed that the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signaling way is important in adversely regulating LPS-induced acute inflammatory responses [85, 86]. Our findings further show that ALA efficiently inhibits acute inflammatory responses by stimulating the PI3K/Akt signaling way. Previously, it was discovered which ALA reduced the expression of LPS-excited cellular adhesion particles and hindered monocyte adherence to people aortic endothelial cells. Treating the rats with wortmannin eliminated all of ALA's anti-inflammatory benefits. In conclusion, ALA may help to avoid sepsis and inflammatory vascular disorders [87]. The effect of ALA on different anti-inflammatory effects is summarized in Fig 5.

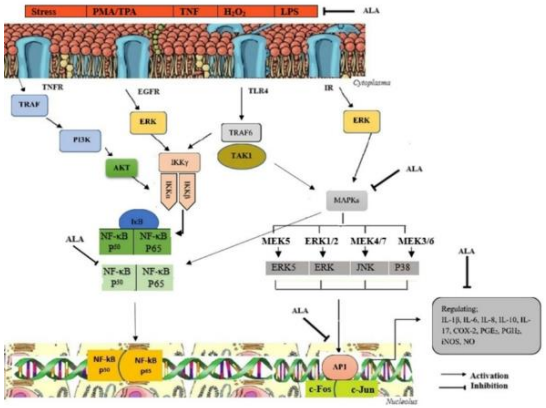

Figure 5. Schematic depiction of possible signalling pathways by which alpha-lipoic acid mitigates inflammation.

ALA-Alpha-lipoic acid; TNF- α- tumor necrosis factor alpha; MAPKs-mitogen-activated protein kinases; TPA- 12-O-tetradecanoylphorbol-13-acetate; IL-interleukin; PMA-phorbol 12-myristate 13-acetate; TLR4-Toll-like receptor 4; H2O2-hydrogen peroxide; IKK-inhibitor-κB kinase; LPS-lipopolysaccharide; NO-nitric oxide; iNOS-inducible nitric oxide synthase; COX-2-cyclooxygenase-2; MyD88-myeloid differentiation factor 88; TRAF6- tumor necrosis factor receptor associated factor 6; IκB-inhibitor kappa B; NF-κBp65-nuclear factor kappa B 3; PGE2-prostaglandin E2; PGH2-prostaglandin 2.

4.3. Antibacterial and anti-biofilm effects.

ALA is a natural coenzyme with remarkable biological activity, showing protective effects against bacteria and viruses. Xia and colleagues have indicated that ALA demonstrates moderate antimicrobial activity [88]. It is was recognized as an antioxidant or a crucial mitochondrion a co-factor, yet the inhibitory properties on bacteria have received little attention [88, 89]. A strain of sakazakii is a gram-negative rod-like bacteria that does not generate spores [90]. The results showed that ALA exhibits antimicrobial activity towards its, with ALA demonstrating its restricting effects by leading to generalized membrane-disrupting effects, leading to increased cell membrane permeability. This was followed by decreased growth of bacteria, alterations in intracellular ATP content, hyperpolarisation of the cell membrane, and a drop in cytoplasm pH. Additionally, field emission scanning electron microscope observations revealed membrane degradation. While ALA demonstrates antimicrobial effects towards its at rather substantial levels, it also holds possibilities for an additive for baby formula and various meals [88]. In another study, the researchers aimed to develop bifunctional scaffolds that promote antibacterial protection while enhancing host cell adhesion and proliferation [91]. Another study compared the antibacterial and potential cytotoxic properties of commercially available uncoated silver nanoparticles (AgNPs) with ALA-coated silver nanoparticles (AgNPsLA) developed by the research team. The findings showed that synthesized AgNPsLA had a better biocompatibility profile and antimicrobial activity compared to uncoated AgNPs. The occurrences are essential for forthcoming in vivo works and the possible medical device applications of AgNPsLA in human use [92]. This study explored the effects of ALA-coated AgNPs on alginate-based aerogels, investigating their potential biomedical applications. The results indicated that ALA-coated AgNPs maintained antimicrobial effects against multidrug-resistant Acinetobacter baumannii and the reference strain Escherichia coli, and they showed improved hemocompatibility compared to a commercially used dressing and polymyxin B [93].

4.4. Antiviral effects.

The brain acts as a parenchymal barrier, defending against pathogens such as viruses that penetrate nervous tissue, which may lead to the removal of viruses through the pathogen-associated molecular pattern (PAMP) pathway [94]. ALA has been proposed as a general neuroprotectant that meets the generally recognized as safe criteria defined by the United States Nutrition & Drug Administration for consumption by individuals [95]. However, the exact effects of ALA, both harmful and beneficial, in the context of brain PAMP events remain unclear. It has been shown that ALA effectively inhibits dsRNA-induced glial cytotoxicity and dysfunctional glutamate transport [24]. In the case of COVID-19, ALA raised intracellular pH, thereby preventing SARS-CoV-2 from entering cells, which further enhanced the host defense against the virus [96]. Influenza A virus (IAV) presents a considerable challenge to the human immune system. A study discovered that ALA therapy improves host immunological modulation, helping with lymphocyte virus clearance without directly influencing viral replication. Furthermore, ALA has been recognized for its therapeutic potential in viral respiratory infections [97]. Vaccinia viruses (VACVs) have been widely employed in smallpox vaccination, but there is now a renewed demand for effective medicines to address these infections. Both etakrinic acid (EA) and ALA reduced vaccinia virus development in vitro in diverse cell types in a dose-dependent manner. EA concentrations were found to be lower, whilst ALA concentrations were greater in the micromolar range [98, 99]. Furthermore, ALA therapy was shown to suppress human immunodeficiency virus (HIV) replication after infection [100]. Finally, ALA demonstrated inhibitory effects on the replication of Viral hemorrhagic septicemia virus. These findings suggest that the antiviral mechanism of ALA may differ between various viruses [98].

4.5. Anti-Alzheimer effects.

Alzheimer's disease (AD) is a severe and degenerative neurological condition that affects neural processes like memory, reasoning, and personality [101, 102]. AD is identified with gradual loss of memory, accompanied by intracellular deposition and extrinsic deposition of aggregated amyloid beta (Aß) protein in the brain of affected individuals [103]. Oxidative

stress is generally related via inflammation and neurodegeneration within AD, as both proinflammatory and anti-inflammatory substances are modulated by oxidative stress and antioxidant responses [104]. Current antioxidant treatments have shown small improvements in AD progression [105]. ALA, a vital cofactor in mitochondrial dehydrogenase reactions, acts as an antioxidant and lessens oxidative stress in elderly animals [22]. Recent experiments proved which the regulation of interleukin-1 beta (IL-1b) and interleukin-6 (IL-6) expression by ALA is associated with changes in DNA methylation of the corresponding promoters, supporting previous research indicating that IL-1b and IL-6 are modulated via methylation of DNA of neuronal models [106]. In addition, studies in neuroblastoma have shown strong protective responses against oxidative stress [107]. The combination of standard anti-inflammatory medications with antioxidant molecules may be a useful approach for developing novel multi-target agents capable of combating both neuroinflammation and oxidative stress, which are criterion aspects with this disorder [108]. Another study investigated whether ALA and its dropped by, DHLA, were present in colonies were regarded along with amyloidosis amino acid, iron, either peroxide from hydrogen. The prior treatment of differentiated basic hippocampus tissues in ALA substantially decreased Aß and Fe/H2O2 toxicities. However, mixing ALA and Fe/H2O2 greatly increased toxicity. The lower cell viability seen in samples treatment by both ALA and Fe/H2O2 was associated leading to higher creation of free radicals. Cortex cells infused with DHLA showed considerable protection towards transportation of glucose decreases caused by Fe/H2O2 or Aß, whereas ALA therapy could not. The data indicate that DHLA, the reduced version of ALA, offers significant protection from Aß- and Fe/H2O2-induced toxic effects. In more detail, the findings show that co-exposure to ALA and Fe/H2O2 greatly enhances oxidative stress. Thus, this research was done concludes that DHLA is an beneficial antioxidant toward Fe/H2O2- and Aß-induced oxidative stress, whereas ALA may exacerbate oxidative stress in iron-rich environments. In the failure of works on the ALA/DHLA balance in the cerebral cortex of people, these findings commit that ALA may have questionable efficacy as an antioxidant in diseases such as AD where iron levels are elevated [22].

4.6. Antiepileptic effects.

Spite of the availability of anti-seizure medications (ASMs) from various molecules and pharmaceutical bands, these drugs fall through achieve seizure check in approximately 20–30% of patient [47, 49, 109, 110] . Oxidative stress in the cerebrum causes oxygen- bonded cellular damage, which plays an important role in the development and continuity of epilepsy [111]. Both in vitro and in vivo studies show that combining anti-seizure drugs with inherently occurring antioxidants, such as ALA, greatly improves therapeutic effectiveness and seizure suppression. However, the precise underlying processes are still to be completely understood [112]. ALA is a key cofactor in mitochondrial dehydrogenase processes and can restore endogenous antioxidants [31]. The findings show that *N*-[(R)-1,2-dithiolane-3-pentanoyl]-L-glutamyl-L-alanine (CMX-2043), an ALA-based medication, may be used as an adjuvant therapy for seizure control and to reduce drug resistance associated with long-term ASM therapy by altering redox signaling. Various in vitro and in vivo proving research on diverse sickness have found that ALA supplementation, coupled with manganese superoxide dismutase overexpression, efficiently scavenges ROS and protects against oxidative stress-related damage. These findings highlight the necessity to conduct more in vitro and in vivo studies to better appreciate the chemicals' potential as supplementary therapeutics within ASM therapy for epilepsy [112].

4.7. Antiparkinsonian effects.

Parkinson's disease (PD) is among the two foremost neurodegeneration condition globally, defined by the gradual death specific neuronal cells [113]. Oxidative stress generated by higher amounts of ROS may cause malfunction and death of cell and neurons, which contribute to disease development [114] ALA, as an antioxidant and iron chelator, has neuroprotective effects in PD; however, the effect of ALA on ferroptosis in PD remains unclear [115]. The protective role of gold nanoparticle/ALA conjugates, through increased mitochondrial ATP production, reduced oxidative degradation of fats in membranes within cells, and biocompatibility, suggests that they could be a promising treatment to alleviate oxidative stress in PD [116, 117] However, given that high concentrations may lead to residual accumulation in organs in vivo, this must be considered when using it in living organisms [116]. ALA may act an anti-ferroptotic function in PD pattern by eliminating excess intracellular iron [118] The combination of ALA and L-DOPA (L-3,4-dihydroxyphenylalanine) improved neurochemical parameters, normalized catalepsy scores, and preserved the integrity of the striatal ultrastructure, demonstrating the benefits of symptomatic and neuroprotective treatment [119, 120]. Additionally, the neuroprotective functions of the R form of alpha-lipoic acid (RLA) on cell survival, cell death, the function of mitochondria, and autophagy were evaluated, and it was concluded that RLA could be an appealing adjuvant for Parkinson's disease [121].

4.8. Anxiolytic effects.

Stress is a common psychological and physical experience in daily life, known to contribute to circulatory diseases and gastrointestinal ulcers [122]. In rats exposed to chronic unpredictable mild stress, ALA partially restored monoamine levels and modulated the 5-hydroxytryptamine 3 receptors receptor exerting an antidepressant effect. Anxiety-like behaviors were prevented by ALA, highlighting its anxiolytic potential. ALA has also been shown to increase tryptophan entry into the brain, thereby enhancing serotonin levels in the synapses. These findings support the use of ALA as an antidepressant [123, 124] More study is needed to find out the efficiency of ALA in models from animals of depression, cognition, and anxiety [123]. Also, ALA has been demonstrated to increase metabolic activity indices, supporting the "selfish brain" idea, which stresses the significance of metabolic alterations in mood disorders [33, 125]. Given the current research, ALA is advised as a dietary supplement to help cope with daily pressures that cause depression-like behavior and cognitive deficiencies [126].

4.9. Effects on schizophrenia.

Schizophrenia is distinguished with symptoms of behavior, dysfunction in the brain, including electroencephalography alterations. Dysregulation of immunological reactions and oxidative disequilibrium have an important part in the etiology of this mental disorder [125]. Further research has demonstrated that ALA effectively reverses both positive and negative schizophrenia-like symptoms induced by repeated ketamine administration, indicating its potential role as an antipsychotic agent [127]. Previous studies incorporating ALA (500-1200 mg) alongside antipsychotic medications in schizophrenia patients have found significant improvements in metabolic profiles [128] However, concerns have been raised about lower red blood cell, white blood cell, and amount of

platelets, highlighting the need for further investigation and caution when prescribing ALA to schizophrenia patients [129].

4.10. Neuroprotective effects.

Neurodegenerative disorders are associated with oxidative tissue damage, leading to a gradual loss of cognitive functions and neuronal cells. Accumulation of oxidative injury in brain mitochondria, proteins, and nucleic acids can contribute to neuronal and cognitive dysfunction [130]. ALA has also proven to be an effective antioxidant in suppressing and treating the study autoimmunity encephalomyelitis, a pet form of multiple sclerosis (MS). Intravenous administration of ALA may be an effective treatment for MS, and more bioavailable ALA formulations with consistent blood levels could serve as potential oral adjunct therapies for MS [21, 22]. Having impaired memory is one of among the most difficult brain disorders. ALA has been used to investigate behavioral and biochemical differences following scopolamine exposure, with data showing significant improvements in behavioral and molecular parameters when exposed to ALA, an antioxidant agent [131]. Elevated extracellular glutamate levels have also been linked to neuronal damage and brain disorders. Notably, ALA's amide analogs (lipoamide and ALA-plus) have been proved it was more successful than ALA in preserving neuronal cells from glutamate-induced toxicity [132]. ALA has also been studied in combination therapies. For instance, the combination of ALA and N-acetylcysteine (NAC) was found to change cognitive impairments in SAMP8 mice, indicating its potential to counteract age-related cognitive decline [133]. Additionally, adding amounts by acetyl-L-carnitine and R-ALA enhanced ability to think and cerebral mitochondria morphology, and oxidative damage biological indicators. These findings suggest that ALA enhances memory task performance by reducing oxidative tress and enhancing the activity of mitochondria [130].

4.11. Antidiabetic effects.

Diabetes-related nephropathy (DN) can be one of the foremost common chronic consequences of diabetic and a main cause of advanced renal disease, which is connected to significant mortality and morbidity [134, 135] Over the past few years, research has increasingly focused on the critical role of podocyte injury in the initiation and progression of diabetic kidney illness [135, 136]. In further studies, a significant reduction in podocyte number and density was reported after the onset of hyperglycemia in diabetic rats, while ALA treatment was shown to prevent podocyte loss, and slow the progression of DN [135, 137] It has been observed that ALA restores insulin- induced glucose uptake in insulin- durable skeletal brawn and significantly reduces plasma glucose levels while increasing insulin-induced glucose uptake in skeletal brawn in streptozotocin-excited diabetic mouse [138, 139] As a potent antioxidant, ALA has been proven to boost neural circulation, lower oxidative stress, and boost distal nerve stimulation in a DN mouse model [140, 141] Likewise, ALA has been shown to reduce fat peroxidation and protein glycation in erythrocytes exposed to high glucose levels [142]. In countries like Germany, ALA is given to treat diabetes-related issues [143]. By reducing glycemia, ALA enhances kidney function, demonstrating its efficacy as a potent antioxidant in diabetes management [134, 144] Dietary supplementation with ALA has been found to mitigate albuminuria and renal pathology associated with diabetic nephropathy in streptozotocin-induced diabetic rats [145–147] Oral administration of ALA may offer protective effects against glomerular podocyte injury in clients with type 2 diabetes [135]. Oral administration of ALA may offer protective effects against glomerular podocyte injury in clients with type 2 diabetes [135]. However, while ALA serves as a nephroprotective agent in DN, it may have potential adverse effects in otherwise healthy kidneys [148]. Clinical trials involving patients with diabetic polyneuropathy indicate that ALA is well-tolerated and beneficial in managing dysesthesia [82]. diabetic patients are more likely to get dry eye sickness [149]. A nano-micelle formulation for ALA drops for the eye has been developed for diabetes-related corneal counseling, which may improve corneal permeability, stability, and solubility [150].

4.12. Anti-allergic effects.

Allergic rhinitis (AR) is a prevalent nasal disorder worldwide, often persisting throughout an individual's lifetime. It is estimated to affect approximately 10–30% of the global population [151]. AR is characterized as an inflammatory condition of the nasal mucosa triggered by allergen exposure, leading to IgE-mediated inflammation. The primary symptoms include sneezing, nasal stuffiness, itchiness, and nasal discharge [152]. A study conducted by Valérie Dardalhon demonstrated that ALA could help alleviate rhinitis by enhancing treg foxp3 (forkhead box P3) expression while simultaneously suppressing transversal relaxation time cytokine production. To examine the possible safety benefits of ALA towards upper respiratory inflammation, researchers developed an ovalbumin (OVA)-provoked AR rat structure. Histopathological evaluations of nose and tissues of the lungs were performed. The administration of ALA significantly reduced nasal effects consist of sniffling and nose rubbing, in addition to lowering serum degree of OVA-exclusive immunoglobulin E (IgE) and immunoglobulin G1(IgG1) [153]. In the current investigation, AR mice treated with ALA exhibited significantly lower serum histamine levels compared to untreated AR mice, staining with H&E revealed a marked increase in infiltrating cells in the rhinal mucosa of the OVA category, whereas this infiltration was majorly reduced in categories cured by ALA or dexamethasone also, giemsa staining confirmed a substantial decrease in eosinophil infiltration within the nasal mucosa of the ALA- and dexamethasone treated groups. Although AR was previously regarded as an inflammation confined to the nasal mucosa, emerging studies suggest that it can lead to systemic airway illness, affecting the whole breathing system [154]. Research suggests that ALA alleviates inflammation in AR mice via activation of the Nrf2/HO-1 process. In other findings, ALA significantly suppressed malondialdehyde levels, further supporting its anti-inflammatory potential. Taken together, these findings suggest that ALA therapy may be a up-and-coming therapeutic approach for the therapy of allergic airway diseases such as AR [155].

4.13. Anticancer effects.

ALA, an organic compound with antioxidant qualities, has promise as an anti-cancer agent due to its potential to reduce apoptosis and inhibition of proliferation of cancer cells were contrasted with healthy cells. ROS have an important role in cancer cell proliferation and death [156]. In a mouse model of subcutaneously implanted SkBr3 cells, dietary ALA retards tumour progression [157]. A mixture of ALA and hydroxycitrate has been observed to lead to tumour growth retardation, similar to that of traditional chemotherapy. More clinical trials are needed [158]. Osteosarcoma (OS) is a type of osseous tumour. Whilst the detailed mechanisms of ALA's anti-cancer activity for OS are not yet clearly understood, evidence from studies has indicated that ALA is a possible prospect in the development of new treatments by OS and deserves further preclinical research [159]. ALA has been evaluated as a potential new therapy for

thyroid cancer and has been found to inhibit cell proliferation and tumour regrowth in thyroid cancer cells. ALA suppressed thyroid cancer cell multiplication by activating AMPK and subsequently downregulating the mTOR (mammalian target of rapamycin)-S6 signalling pathway [160]. ALA was also supposed to prevent development of tumour-forming ovarian epithelial cells, though it did not affect surface epithelial cells. The combined therapy with ALA reduced cell invasion and tumour cell adhesion for the first 24 hours, but its anti-tumour effect was seen to diminish after 48 hours [161]. Both ALA and its reducing form, DHLA, effectively induced cell death in people colon cancer cells via a pro-oxidant system with increasing mitochondrial uptake of oxidisable materials [162]. Moreover, to boost the anticancer activity of 2-methoxyestradiol against breast cancer, ALA nanoparticles were established as a delivery vehicle for controlling breast cancer cell growth [163].

4.14. Effect on autophagy.

Autophagy is a key molecular process that facilitates the elimination of damaged or malfunctioning cellular components [15, 16]. ALA activates AMPK promoting autophagy through ULK1 phosphorylation. It is demonstrated to alleviate various factors that cause cell damage by inhibiting autophagy through different pathways [17, 18]. It has been reported to contribute significantly to autophagy and apoptotic pathways by activating the H2O2-induced decreased expression of AKT, PI3K and ERK, which are key regulators of pathways involved in survival. ALA activates AMPK, promoting autophagy through ULK1 phosphorylation [18,19,56,126]. It is demonstrated to alleviate various factors that cause cell damage by inhibiting autophagy through different pathways (Fig 5).

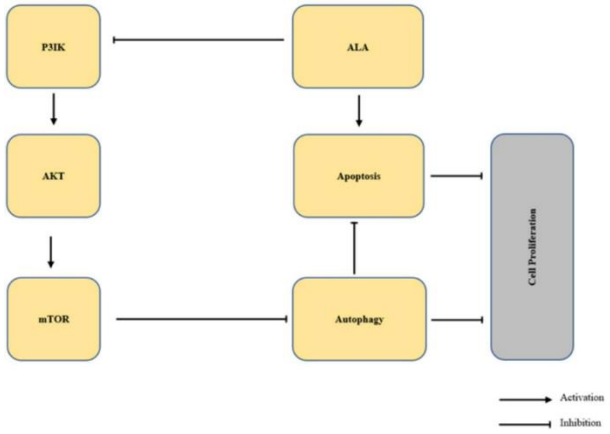

Figure 5. Regulation of autophagy and apoptotic pathways by alpha-lipoic acid.

Alpha-lipoic acid-ALA; phosphoinositide-3-kinase-P3IK; Ser/Thr kinase-AKT (also known as protein kinase B)

4.15. Osteoprotective effects.

Osteoporosis (OP) is a systemic osseous illness defined with low bone block and degradation of the microarchitecture of bone texture, leading to a rised venture of fracture [164]. It is defined by reduced bone mass and the degradation of bone microarchitecture, commonly observed in the elderly, particularly in post-menopausal women. [165] In additional research, we investigated the protective efficacy of ALA against AMA (anti-mitochondrial antibody)-induced cytotoxicity using the MC3T3-E1 osteoblast-like cell line, and our results revealed that ALA treated osteoblasts dose-dependently reduced AMA-induced cytotoxicity and LDH (lactate dehydrogenase) release, showing a beneficial effect. In parallel, ALA has been noticed to prohibit steroid-induced osteonecrosis in bunnies [166]. Furthermore, ALA supplementation was found to support femoral fracture healing [167]. . In another study, discovered which ALA embarrassed osteoclastogenesis in bone marrow-reproduce precursor cell cultures below osteoclastogenic terms [168, 169] ALA exerts bone-preventive impacts with increasing the osteoprotegerin/ RANK ligand mRNA rate both in vivo and in vitro [170]. Alendronate (AL), a widely used amino-bisphosphonate in drug treatment for OP, conjugates to AuÅPs surfaces via ALA, and the developed AuÅPs-AL demonstrate excellent stability, biocompatibility, and bone-targeting capabilities. These nanoparticles can potentially accelerate the osteogenesis process, partially through activation of the Wnt/β-catenin signaling way. Our study emphasizes the great potential of AuÅPs-AL for future biomedical applications related to bone tissue engineering [171–173] Recently, accumulating evidence has shown a close association between oxidative stress, apoptosis, and glucocorticoid-induced osteoporosis (GIOP). ALA can prevent GIOP by antagonizing oxidative stress and suppressing apoptosis, thus supporting bone formation [174, 175].

4.16. Cardioprotective effects.

Cardiac and bloodstream diseases, often referred to as cardiovascular disorders, were crucial health problems [176]. ALA has been shown to reduce fructose-induced hypertension and prevent increased superoxide anion production in heart mitochondria, as well as the formation of succeeded glycation end-products (AGEs) in the aortas of glucose-treated mouse [177] Although the role of ALA in protecting against cardiovascular hypertrophy is not yet fully understood, studies have demonstrated that ALA effectively improves both in vivo and in vitro models of cardiac hypertrophy [178] Combination therapies involving ALA have also been investigated. For example, co-administration of ALA with MitoQ (coenzyme Q10) was found to stabilize blood pressure fluctuations, prevent excessive mitochondrial membrane depolarization, improve myocardial function, enhance mitochondrial fusion gene expression, and strengthen the endogenous antioxidant system [179]. Additionally, a palladium-alpha-lipoic acid formulation (POLY-MVA) was demonstrated the role of a vital role in age-related myocardial antioxidant protection [180].

4.17. Hepatoprotective effects.

Microcystins, toxins synthesized by cyanobacteria, pose a threat to the antioxidant defense system of living organisms, particularly affecting the liver. Oxidative stress contributes to many pathological conditions in the liver [181]. ALA prevents liver oxidative damage by activating Nrf2 signaling and increasing glutathione stages, which diminishes by aging in hepatocytessco[182] ALA intervention reduces liver aspartate aminotransferase and alanine aminotransferase stages, meaning its ability to mitigate fluoride-induced oxidative damage, inhibit Wnt/Ca2+ pathway activation, and improve mitochondrial dynamics and biogenesis [183]. Additionally, priming adipose-derived stem cells with ALA has been reported to enhance cell viability, manage cell membrane damage and apoptosis, and reduce ROS production, thereby improving hepatocyte response during fibrotic and oxidative stress conditions. The results show that ALA could serve as a possible preventative and medical therapy to fluorotoxic liver damage [50] In obese illness via not alcoholic fat liver damage, supplementation with 1200 mg of ALA daily was found to have positive impacts on serum adiponectin, IL-6 levels, and hepatic steatosis [177]. Lastly, the combination of

ALA with aminoguanidine has been found to exhibit additional anti-lipidemic properties, further enhancing its hepatoprotective potential [184].

4.18. Effects on the kidneys.

It has been proven that ALA also provides kidney protection by antagonizing inflammatory stresses in kidney tissues [185]. The kidney podocyte protection attributed to ALA may be partly related to its effects in preventing excessive synthesis of ROS and increasing in vivo antioxidant capacity, independently of glycemic check in diabetics clients [135]. DN is a major chronic consequence of diabetes, and oxidative damage and accompanying degradation of vascular endothelial integrity are likely to take on a crucial part in its development [133, 186] Long-term ALA application was scientifically proven to boost kidney dysfunction [133] Short-term ALA may protect the kidneys against general oxidative stress in early DN, and the emergence of CD63-positive exosomes in urine could be a new biological marker for early recognition and therapy prediction in diabetes [134]. Currently, ALA is extensively utilized in clinical practice for diabetic peripheral neuropathy, which is widely accepted for kidney protection [135].

4.19 Anti-obesity effects.

Taking supplements to eicosapentaenoic acid (EPA) or ALA, either alone or in combinations, has been demonstrated via research to help in losing weight when taken in conjunction with a diet with fewer calories. The rise in obesity prevalence has emerged as a significant global health issue affecting both adults and children, including teenagers [187]. A daily 300 mg dosage of ALA paired by an energy-restricted diet has been shown to increase loss of weight and decrease fat mass [188] Sirtuin 1 (SIRT1) is a protein related with length that controls metabolism of calories as well lifetime in reaction to dietary deficiency. ALA exhibits overweight by stimulating the SIRT1/AMPK signalling path. In addition to promoting fatty acid oxidation, ALA also modulates fatty acid synthase (FAS) and adipose triglyceride lipase (ATGL) expression, contributing to lipid reduction. Oral ALA administration has been shown to decrease body weight and visceral fat content [28]. Furthermore, ALA induces a "browning" effect in white adipose tissue, which may enhance its anti-obesity properties and support metabolic health [189]. Additionally, ALA promotes significant weight loss by increasing energy expenditure and reducing hypothalamic AMPK exercise and consuming food. This suggests that ALA might be an appealing anti-obesity agent, in the care of leptin-resistant overweight individuals [190]. When combined with exercise, ALA has been shown to counteract atherogenic effects, further supporting its role in weight management and metabolic health [191].

4.20. Anti-aging effects.

It is thought that a species' longevity is governed on the amount of harm to mitochondria generated with radicals that are free throughout regular metabolism [192] Lipid peroxidation and antioxidant levels were assessed prior to and after DL-ALA addition in the liver and kidney mitochondria of young and aged rats. In elderly rats treated with DL-ALA, lipid peroxidation levels were reduced while antioxidant status increased [193]. The results suggest that (R)-ALA addition could be a healthy and productive tool for improving overall metabolic activity and increasing antioxidant status, while also providing enhanced defense towards both oxidative and xenobiotic damage as years increases [33]. In light of these results, lipoic acid supplementation appears to become a successful medicinal product for treating age-related disorders [193].

4.21. Effects on the gastrointestinal system.

Mucositis is a chronic inflammatory illness that causes ulcers and inflammatory of the gastrointestinal mucosal [182]. ALA was used in a mucositis model induced by 5-fluorouracil (5-FU), and as a result, structural improvement in intestinal damage to the mucosal was observed within the teams injected with ALA. Subsequently, the inclusion of ALA in 5-FU treatment has been considered a possible choice for cancer clients suffering gastritis [194]. Additionally, it has been previously reported that ALA has protective effects on ulcers and gastrointestinal tissues [195, 196] In another study, the impacts of ALA on indomethacin-induced gastric ulcers were evaluated, and ALA showed a significant gastric protective effect. This anti-ulcer impact of ALA can be ascribed to its antioxidant and anti-inflammatory activities [195].

4.22. Effects on the respiratory system.

Asthma is a diverse respiratory illness that affects 300 million individuals globally [197]. Oxidative damage is a older participator to airway inflammation in asthma, and ALA may be an effective adjuvant treatment in bronchial asthma. Furthermore, we discovered that the effects of ALA are related with lower function of the redox-sensitive transcribed factor nuclear factor kappa B (NF-κB) [53, 198]. Exposure to tobacco smoke during pregnancy leads to oxidative damage in the lung tissues of offspring, causing changes in lung development. ALA administration appears to provide limited protective effects against this oxidative stress in neonatal lung development, and these findings suggest that controlled and conscious supplementation of ALA may partially reduce this damage [199]. In both in vivo and in vitro experiments, there is strong argument showing that ALA suppresses lung cancer growth and the viability of lung cancer cells. Based on the data, ALA may serve as an alternative therapeutic approach for lung cancer in humans [186].

4.23. Effects on the immune system.

Vitamin C or E, and ALA are powerful dietary antioxidants that aid in immunological function. According to studies, ALA enhances antioxidant enzyme activity in the presence of dexamethasone-induced oxidative damage. As a result, vitamin C, E, and ALA help regulate both enzymatic and non-enzymatic defense mechanisms [200]. ALA has been found to alleviate oxidative stress and immune alterations caused by aflatoxin B1, at least in part, by modulating the inflammatory response through changes in pro-inflammatory cytokines examples include IL-6 and TNF-α [201]. Additionally, everyday mouth dose of ALA at the moment of immunisation greatly reduced the course of experimental autoimmune encephalomyelitis (EAE), a multiple sclerosis type. That effect has been related to a decline in infiltrating T cells, macrophages, and demyelination within the central nervous system [202]. Intraperitoneal (IP) injection of ALA also halted disease development. Furthermore, at very high concentrations, ALA inhibited proteolytic activity. This study found that ALA significantly reduces IFN-γ (Interferon-gamma) and IL-4 (Interleukin-4) made with encephalitogenic T cells [203].

4.24. Effects on The Reproductive System

4.24.1 Effects against pregnancy-loss risk.

ALA is a safe native molecule which acts a role within the immunomodulation of very physiological processes. It has

become published that orally administered ALA treats various inflammatory pathologies and supports pregnancy. For the first time, it was observed that ALA, when applied vaginally, was well absorbed and dispersed in the vaginal and uterus layers and did no effect on the insertion ratio or the amount of implanted mediation in the reproductive tissue. Moreover, ALA delayed the duration of labor and reversed the increased levels of pro-inflammatory cytokines in the uterine tissue. Further animal and human studies are recommended to explore the mechanism of ALA's effect in the care of premature birth. Yet, the initial results provide intriguing evidence for suggesting genital ALA in obstetrics as a novel way to ensuring physiologic pregnancy. Additionally, ALA is associated with its ability to counteract pathological changes in the complex networks of cytokines, chemokines, and growth factors, and to restore their physiological conditions. ALA supplementation has been shown to significantly accelerate the restoration process of physiological conditions in threatened pregnancy and improve the health disorders of both the mother and fetus [25, 75]. Sexual hormone insufficiency is linked to metabolic alterations, oxidative stress, or subclinical inflammation to postmenopausal women. It is proposed that NAC and ALA may mitigate many of the negative consequences of reproductive hormone depletion via estrogen-independent pathways [204]. Carbamazepine exposure during pregnancy has an unfavorable effect on the epididymis. Yet, ALA's antioxidant, anti-apoptotic, and steroidogenic features enhanced epididymal activity and sperm fertilization potential [205].

4.24.2. Effects on infertility.

Infertility is defined as the failure of pregnancy after a year of basic, informal sexual activity [206]. Investigations have demonstrated that sperm cells are capable of producing ROS at different stages of growth. Increased synthesis of ROS by the leukocytes in testosterone, plus the existence of faulty spermatozoa, may trigger being infertile[207]. New evidence demonstrates that ALA has the ability to improve sperm circulation while decreasing sperm harm to DNA, resulting in greater male fertility [208]. Also, ALA improves egg maturing, embryo growth, and reproductive performance [209] Periodic ALA consumption has been shown to alleviate the pelvic discomfort related to endometriosis and normalize menstruation blood circulation. As consequently, ALA is viewed as a viable treatment for infertility, necessitating more tests in the clinic. Besides, ALA has been identified for its preventive role against various kinds of variables that can disrupt female reproductive health [210].

4.24.3. Effects on polycystic ovary syndrome.

The blend of ALA (400 mg/day) with myo-inositol (1 mg/day) has demonstrated success in the therapy of polycystic ovarian syndrome (PCOS) [211]. This blend improves the duration of menstruation in people with PCOS [212] Blending D-chiro-inositol and ALA may dramatically enhance the metabolism of women with PCOS [213] In PCOS, ALA lowers stress caused by oxidation and glucose resistance. Likewise, a mixture of NAC, ALA, and bromelain may help prevent and heal endometriosis. ALA may also be used to avoiding diabetes embryopathy and inflammation-induced premature breakdown of membranes in embryos. In the end, ALA might be used safely as a dietary supplement whilst pregnant and as a medication for neural pain [209].

4.25. Toxicity effects.

ALA is a mighty antioxidant used to treat various disorders. Although ALA is considered a safe supplement and poisoning is rarely seen, acute high doses can be fatal. When acute toxicity occurs, neurological effects, metabolic acidosis, and T-wave inversions in the electrocardiogram are observed [214]. For example, after an unintentional high dose (toxicological tests show an ALA serum concentrate of 10.280 µg/L) intravenous supplementation, the patient was at up danger due to Poor platelets, extended prothrombin and thromboplastin times, and symptoms of brought up C-reactive protein, abnormally high ferritin, and the onset of liver failure [215]. ALA dietary additives are commonly used in clinical practice, but protection evaluations are insufficient [216]. Anaphylactic shock or reactions occurring in the first week of supplementation have also been reported [217]. Clinicians should closely monitor patients treated with ALA-containing products, diagnose potential side effects promptly, and discontinue use immediately if necessary [216]. ALA is a powerful antioxidant that promotes kidney function by lowering glucose levels in diabetes. However, the precise processes behind ALA's antioxidant benefits are not entirely known. For example, whereas ALA protects the kidneys in diabetic nephropathy, it may be toxic in healthy kidneys. As a result, monitoring the dose, treatment duration, and potential side effects of ALA supplementation in healthy kidneys is critical. It has been determined that ALA can have. The instances of pro-oxidant and antioxidant actions rely on the fundamental physical and metabolic circumstances [148]. In conclusion, based on the studies, it is observed that ALA has almost no toxic effects at therapeutic doses used, but minimal toxic effects at high doses.

5. Conclusions

ALA is a naturally occurring fatty acid that serves as a vital, covalently bonded cofactor in numerous enzyme processes, including alpha-ketoacid dehydrogenases, which are required for mitochondrial energy metabolism. Mitochondria produce enough ALA from octanoic acid, and this dithiol fatty acid is also found in several meals. It can be assimilated in the intestines and disseminated to many organs and tissues, including the brain kidneys and liver. Although these pharmacological effects have been observed in vitro and animals, it remains uncertain if alpha lipoic acid supplements have clinically significant effects in humans. The optimal dose of ALA in oral form has not yet been fully determined. ALA administration has not shown beneficial effects at doses of 100-1200 mg/day, with dose-related trends on total symptom score and overall satisfaction. Alpha lipoic acid is presently offered in tablet and capsule forms, including 50 to 600 mg, with the advised dosage varying from 100 to 600 mg once or twice a day. Alpha lipoic acid is generally well tolerated; nevertheless, elevated doses may result in adverse symptoms such as abdominal discomfort, heartburn, constipation or diarrhea, nausea, dizziness, and headache. Numerous studies on alpha lipoic acid in patients with cardioprotective, hepatoprotective, diabetic polyneuropathy, arthritis, diabetes, fibromyalgia, reproductive system multiple sclerosis, osteoarthritis, and other conditions have produced inconsistent results, yet almost always with minimal or negligible adverse effects.

Pharmacokinetically, ALA has an oral bioavailability of roughly 30% due to its brief blood half-life, significant presystemic clearance, and hepatic first-pass metabolism. While this bioavailability appears adequate for the biological effects of ALA, new studies indicate that its bioavailability is enhanced through various formulations. The data obtained

show that ALA liquid formulations have higher plasma concentrations and therefore bioavailability compared to solid dosages. Alpha lipoic acid is a biologically active ingredient widely used in the clinic in different pharmaceutical forms, multivitamin tablets, multivitamin capsules and food supplements. While purported to have antioxidant, anti-inflammatory, antimicrobial, anti-Alzheimer, antiepileptic, antiparkinsonian, anxiolytic, effects on schizophrenia, neuroprotective, antidiabetic, antiallergic, anticancer, anti-osteoporosis, cardioprotective, hepatoprotective, anti-obesity, anti-aging, reproductive system, and so on, it has not been approved by the EMA and FDA as therapy for any medical disease or condition. ALA holds great promise in the creation of new medical interventions for treating human diseases. However, despite its potential, further extensive research is still needed to clarify ALA's possible molecular therapeutic effects through long-term human clinical trials.

Author Contributions: Oruc Yunusoglu and Esma Koyuncu writing the text of the paper, Oruc Yunusoğluı and Esma Koyuncu discussion of the material, editing the text of the paper, Oruc Yunusoglu concept and supervision of the study, editing text of the paper.

Funding: This work was not supported by any funding, and no additional grants were obtained.

Informed Consent Statement: This article does not contain any studies involving human participants or animals performed by any of the authors.

Conflicts of Interest: The authors of this work declare that they have no conflict of interest

References

1. Morikawa, T., Yasuno, R., and Wada, H. Do mammalian cells synthesize lipoic acid? Identification of a mouse cDNA encoding a lipoic acid synthase located in mitochondria, FEBS Letters **2001,** 498, 16-21, doi.org/10.1016/S0014-5793(01)02469-3.

2. Onder, N. T., Alcay, S., and Nur, Z. Effects of alpha-lipoic acid on ram semen cryopreservation and post-thaw life span, Andrologia **2022,** 54, e14249, doi.org/10.1111/and.14249.

3. Salehi, B., Yılmaz, B., Antika, G., Boyunegmez, T. T., Fawzi, M., and Sharifi-Rad, J. Insights on the use of α-lipoic acid for therapeutic purposes, Biomolecules **2019,** 9, 356, doi.org/10.3390/biom9080356.

4. Tibullo, D., Li Volti, G., Giallongo, C., Grasso, S., Tomassoni, D., and Bramanti, V. Biochemical and clinical relevance of alpha lipoic acid: antioxidant and anti-inflammatory activity, molecular pathways and therapeutic potential, Inflammation Research **2017,** 66, 947–959, doi.org/10.1007/s00011-017-1079-6.

5. Nikolić, R. S., Krstić, N. S., Nikolić, G. M., Kocić, G. M., and Signelković, D. H. Molecular mechanisms of beneficial effects of lipoic acid in copper intoxicated rats assessment by FTIR and ESI-MS, Polyhedron **2014,** 80, 223-227, doi.org/10.1016/j.poly.2014.04.033.

6. Baumgartner, M. R., Schmalle, H., and Dubler, E. The interaction of transition metals with the coenzyme α-lipoic acid: synthesis, structure and characterization of copper and zinc complexes, Inorganica Chim. Acta **1996,** 252, 319-331, doi.org/10.1016/S0020-1693(96)05331-5.

7. Uchida, R., Okamoto, H., Ikuta, N., and Hirota, T. Enantioselective pharmacokinetics of α-lipoic acid in rats, Int. J. Mol. Sci. **2015,** 16, 22781-22794, doi.org/10.3390/ijms160922781.

8. Devasagayam, T. P. A., Subramanian, M., and Sies, H. Prevention of singlet oxygen-induced DNA damage by lipoate, Chem. Biol. Interact. **1993,** 86, 79-92, doi.org/10.1016/0009-2797(93)90113-D.

9. Tripathi, A. K., Ray, A. K., Mishra, S. K., Bishen, S. M., and Khurana, A. Molecular and therapeutic insights of alpha-lipoic acid as a potential molecule for disease prevention, Rev. Bras. Farmacogn. **2023,** 33, 272–287, doi.org/10.1007/s43450-023-00370-1.

10. Rezaei, Z. S., Hasani, M., Morvaridzadeh, M., Beatriz, P. A., Heydari, H., and Heshmati, J. Effect of alpha-lipoic acid on oxidative stress parameters: a systematic review and meta-analysis, J. Funct. Foods **2021,** 87, 104774, doi.org/10.1016/j.jff.2021.104774.

11. Monastra, G., De Grazia, S., and Unfer, V. Immunomodulatory activities of alpha lipoic acid with a special focus on its efficacy in preventing miscarriage, Expert Opin. Drug Deliv. **2016,** 13, 1695-1708, doi.org/10.1080/17425247.2016.1200556.

12. Cremer, D. R., Rabeler, R., and Lynch, B. Safety evaluation of α-lipoic acid (ALA), Regul. Toxicol. Pharmacol. **2006,** 46, 29-41, doi.org/10.1016/j.yrtph.2006.06.004.

13. Ou, P., Tritschler, H. J., and Wolff, S. P. Thioctic (lipoic) acid: a therapeutic metal-chelating antioxidant? Biochem. Pharmacol. **1995,** 50, 123-126, doi.org/10.1016/0006-2952(95)00116-H.

14. Spector, A., Huang, R. R. C., and Wang, R. R. Thioredoxin fragment 31-36 is reduced by dihydrolipoamide and reduces oxidized protein, Biochem. Biophys. Res. Commun. **1988,** 150, 156-162, doi.org/10.1016/0006-291X(88)90499-8.

15. Guseva, E. A., Pavlova, J. A., and Sergiev, P. V. Synthetic activators of autophagy, Biochemistry (Moscow) **2024,** 89, 27–52, doi.org/10.1134/S0006297924010024.

16. Pavlova, J. A., Guseva, E. A., and Sergiev, P. V. Natural activators of autophagy, Biochemistry (Moscow) **2024,** 89, 1–26, doi.org/10.1134/S0006297924010012.

17. Bossio, S., Perri, A., Gallo, R., and Aversa, A. Alpha-lipoic acid reduces cell growth, inhibits autophagy, and counteracts prostate cancer cell migration and invasion: evidence from in vitro studies, Int. J. Mol. Sci. **2023,** 24, 17111, doi.org/10.3390/ijms242317111.

18. Peng, P., Zhang, X., Qi, T., Cheng, H., Kong, Q., and Ding, Z. Alpha-lipoic acid inhibits lung cancer growth via mTOR-mediated autophagy inhibition, FEBS Open Bio. **2020,** 10, 607–618, doi.org/10.1002/2211-5463.12820.

19. Stoll, S., Hartmann, H., Cohen, S. A., and Müller, W. E. The potent free radical scavenger α-lipoic acid improves memory in aged mice: putative relationship to NMDA receptor deficits, Pharmacol. Biochem. Behav. **1993,** 46, 799-805, doi.org/10.1016/0091-3057(93)90204-7.

20. Stoll, S., Rostock, A., Bartsch, R., Korn, E., and Müller, W. E. The potent free radical scavenger α-lipoic acid

improves cognition in rodents, Ann. N. Y. Acad. Sci. **1994,** 717, 122-128, doi.org/10.1111/j.1749-6632.1994.tb12079.x.

21. Xu, C., Li, E., Liu, S., Huang, Z., and Chen, L. Effects of α-lipoic acid on growth performance, body composition, antioxidant status and lipid catabolism of juvenile Chinese mitten crab Eriocheir sinensis fed different lipid percentage, Aquaculture **2018,** 484, 286-292, doi.org/10.1016/j.aquaculture.2017.09.036.

22. Lovell, M. A., Xie, C., Xiong, S., and Markesbery, W. R. Protection against amyloid beta peptide and iron/hydrogen peroxide toxicity by alpha lipoic acid, J. Alzheimer's Dis. **2003,** 5, 229-239, doi.org/10.3233/JAD-2003-5306.

23. Fiedler, S. E., Yadav, V., Kerns, A. R., Tsang, C., Markwardt, S., and Salinthone, S. Lipoic acid stimulates cAMP production in healthy control and secondary progressive MS subjects, Mol. Neurobiol. **2018,** 55, 6037-6049, doi.org/10.1007/s12035-017-0813-y.

24. Scumpia, P. O., and Stevens, B. R. Alpha-lipoic acid effects on brain glial functions accompanying double-stranded RNA antiviral and inflammatory signaling, Neurochem. Int. **2014,** 64, 55-63, doi.org/10.1016/j.neuint.2013.11.006.

25. Micili, S. C., Goker, A., Kuscu, K., and Fuso, A. α-lipoic acid vaginal administration contrasts inflammation and preterm delivery in rats, Reproductive Sci. **2019,** 26, 128-138, doi.org/10.1177/1933719118766266.

26. Suh, J. H., Shenvi, S. V., and Hagen, T. M. Decline in transcriptional activity of Nrf2 causes age-related loss of glutathione synthesis, which is reversible with lipoic acid, Proc. Natl. Acad. Sci. U. S. A. **2004,** 101, 3381-3386, doi.org/10.1073/pnas.0400282101.

27. Kozlov, A. V., Gille, L., Staniek, K., and Nohl, H. Dihydrolipoic acid maintains ubiquinone in the antioxidant active form by two-electron reduction of ubiquinone and one-electron reduction of ubisemiquinone, Arch. Biochem. Biophys. **1999,** 363, 148-154, doi.org/10.1006/abbi.1998.1064.

28. Chen, W. L., Kang, C. H., and Lee, H. M. α-lipoic acid regulates lipid metabolism through induction of Sirtuin 1 (SIRT1) and activation of AMP-activated protein kinase, Diabetologia **2012,** 55, 1824-1835, doi.org/10.1007/s00125-012-2530-4.

29. Smith, A. R., Shenvi, S. V., Widlansky, M., and Hagen, T. M. Lipoic acid as a potential therapy for chronic diseases associated with oxidative stress, Curr. Med. Chem. **2012,** 11, 1135-1146, doi.org/10.2174/0929867043365387.

30. Zhang, W. J., Bird, K. E., and Frei, B. Dietary α-lipoic acid supplementation inhibits atherosclerotic lesion development in apolipoprotein e-deficient and apolipoprotein e/low-density lipoprotein receptor-deficient mice, Circulation **2008,** 117, 421-428, doi.org/10.1161/CIRCULATIONAHA.107.725275.

31. Packer, L., Witt, E. H., and Tritschler, H. J. Alpha-lipoic acid as a biological antioxidant, Free Radic. Biol. Med. **1995,** 19, 227-250, doi.org/10.1016/0891-5849(95)00017-R.

32. Abdulghani, M., and Naser, A. Estimation of pharmacokinetic parameters of alpha-lipoic acid in the chicks model, Baghdad J. Biochem. Appl. Biol. Sci. **2022,** 3, 122-132, doi.org/10.47419/bjbabs.v3i02.91.

33. Hagen, T. M., Ingersoll, R. T., and Ames, B. N. (R)-α-Lipoic acid-supplemented old rats have improved mitochondrial function, decreased oxidative damage, and increased metabolic rate, The FASEB Journal **1999,** 13, 411-418, doi.org/10.1096/fasebj.13.2.411.

34. Murali, P., George, S. K., and Dominic, G. Effect of dietary supplementation of l-carnitine on serum lipid profile and antioxidant status in broiler chicken fed with animal fat-rich diet, Appl. Biol. Res. **2020,** 22, 118-122, doi.org/10.5958/0974-4510.2020.00018.9.

35. Banik, S., Halder, S., and Onoue, S. Self-emulsifying drug delivery system of (R)-α-lipoic acid to improve its stability and oral absorption, Biopharm. Drug Dispos. **2021,** 42, 226-233, doi.org/10.1002/bdd.2277.

36. Brufani, M. α-lipoic acid: drug or dietary supplement? An overview on the pharmacokinetics, available formulations and clinical evidence in the diabetes complications, Progress in Nutrition **2014,** 16, 62-74, doi.org/10.23751/pn.v19i1.6325.

37. Hermann, R., Mungo, J., and Ziegler, D. Enantiomer-selective pharmacokinetics, oral bioavailability, and sex effects of various alpha-lipoic acid dosage forms, Clin. Pharmacol. **2014,** 6, 195–204, doi.org/10.2147/CPAA.S71574.

38. Bustamante, J., Lodge, J. K., Marcocci, L., Tritschler, H. J., and Rihn, B. H. α-lipoic acid in liver metabolism and disease, Free Radic. Biol. Med. **1998,** 24, 1023-1039, doi.org/10.1016/S0891-5849(97)00371-7.

39. Wepierre, J., Corroller, M., and Dupuis, D. In vivo cutaneous distribution of linoleic acid following topical application in the hairless rat, J. Soc. Cosmet. Chem. Jpn. **1986,** 37, 191-198, doi.org/10.1007/bf00455174.

40. Wepierre, J., Corroller, M., and Didry, J. R. Distribution and dissociation of benzoyl peroxide in cutaneous tissue after application on skin in the hairless rat, Int. J. Cosmet. Sci. **1986,** 8, 97-104, doi.org/10.1111/j.1467-2494.1986.tb00437.x.

41. Podda, M., Rallis, M., Traber, M. G., and Maiboch, H. I. Kinetic study of cutaneous and subcutaneous distribution following topical application of [7,8-14C]rac-α-lipoic acid onto hairless mice, Biochem. Pharmacol. **1996,** 52, 627-633, doi.org/10.1016/0006 2952(96)00337-1.

42. Teichert, J., Hermann, R., and Preiss, R. Plasma kinetics, metabolism, and urinary excretion of alpha-lipoic acid following oral administration in healthy volunteers, J. Clin. Pharmacol. **2003,** 43, 1257-1267, doi.org/10.1177/0091270003258654.

43. Angelucci, L., and Mascitelli-Coriandoli, E. Anticholesterol activity of α-lipoic acid, Nature **1958,** 182, 911-912, doi.org/10.1038/182396b0.

44. Brufani, M., and Figliola, R. (R)-α-lipoic acid oral liquid formulation: pharmacokinetic parameters and therapeutic efficacy, Acta Biomedica **2014,** 85, 108-115, PMID: 25245645.

45. Teichert, J., Tuemmers, T., Achenbach, H., Preiss, C., and Preiss, R. Pharmacokinetics of alpha-lipoic acid in subjects with severe kidney damage and end-stage

renal disease, J. Clin. Pharmacol. **2005,** 45, 313-328, doi.org/10.1177/0091270004270792.

46. Akünal, T. C., and Yunusoğlu, O. Oleanolic acid suppresses pentylenetetrazole-induced seizure in vivo, Int. J. Environ. Health Res. **2023,** 33, 529–540, doi.org/10.1080/09603123.2023.2167947.

47. Berköz, M., Yunusoğlu, O., and Bozkurt, A. Investigation of antiepileptic potentials of usnic acid and some lichen species on the behavioral and biochemical levels in pentylenetetrazole-induced kindling model of epilepsy, J. Res. Pharm. **2024,** 28, 1378–1390, doi.org/10.29228/jrp.816.

48. Yunusoğlu, O., Ayaz, İ., & Dovankaya, E. H. Pharmacological, medicinal and biological properties of flavonoids: A comprehensive review. Journal of Research in Pharmacy **2025,** 29(2), 561-584. doi.org/10.12991/jrespharm.1661054

49. Sevindik, M., Krupodorova, T., Sevindik, E., Koçer, O., Uysal, I., & Ünal, O. Elaeagnus angustifolia L.: A Comprehensive Review of Its Biological Activities, Phenolic and Chemical Constituents, and Applications. Applied Fruit Science **2025,** 67(2), 70, doi.org/10.1007/s10341-025-01294-x.

50. Lasota, M., Jankowski, D., Wiśniewska, A., Szeleszczuk, Ł., Misterka-Kozaka, A., Kaczor-Kamińska, M., ... & Brzozowski, T. Interaction of avapritinib with congo red in pancreatic cancer cells: molecular modeling and biophysical studies. International Journal of Molecular Sciences **2025,** 26(5), 1980. doi.org/10.3390/ijms26051980.

51. Shay, K. P., Moreau, R. F., Smith, E. J., and Hagen, T. M. Alpha-lipoic acid as a dietary supplement: molecular mechanisms and therapeutic potential, Biochim. Biophys. Acta Gen. Subj. **2009,** 1790, 1149–1160, doi.org/10.1016/j.bbagen.2009.07.026.

52. Peng, P., Zhang, X., Qi, T., Cheng, H., Kong, Q., and Ding, Z. Alpha-lipoic acid inhibits lung cancer growth via mTOR-mediated autophagy inhibition, FEBS Open Bio. **2020,** 10, 607–618, doi.org/10.1002/2211-5463.12820.

53. Hassan, A., Ibrahim, A., Mbodji, K., Coëffier, M., Ziegler, F., and Marion-Letellier, R. An α-linolenic acid-rich formula reduces oxidative stress and inflammation by regulating NF-κB in rats with TNBS-induced colitis, J. Nutr. **2010,** 140, 1714-1721, doi.org/10.3945/jn.109.119768.

54. Kütter, M. T., Monserrat, J. M., Primel, E. G., and Tesser, M. B. Effects of dietary α-lipoic acid on growth, body composition and antioxidant status in the plata pompano Trachinotus Marginatus (Pisces, Carangidae), Aquaculture **2012,** 368–369, 29–35, doi.org/10.1016/j.aquaculture.2012.09.010.

55. Cruz, L. C., Josende, M. E., Tavares, P. B., Wasielesky, W., and Maciel, F. E. Lipoic acid modulates energetic metabolism and antioxidant defense systems in Litopenaeus Vannamei under hypoxia/reoxygenation conditions, Aquaculture **2018,** 497, 396–404, doi.org/10.1016/j.aquaculture.2018.08.020.

56. He, M., Wu, Y., Hong, M., Yun, Z., and Jiang, Y. α-Lipoic acid treatment alleviates postharvest pericarp browning of litchi fruit by regulating antioxidant ability and energy metabolism, Postharvest Biol. Technol. **2021,** 180, 111629, doi.org/10.1016/j.postharvbio.2021.111629.

57. Turk, H., Erdal, S., Karayel, U., and Dumlupinar, R. Attenuation of lead toxicity by promotion of tolerance mechanism in wheat roots by lipoic acid, Cereal Res. Commun. **2018,** 46, 424–435, doi.org/10.1556/0806.46.2018.020.

58. Monserrat, J. M., Garcia, M. L., Ventura-Lima, J., González, M., Ballesteros, M. L., and Wunderlin, D. A. Antioxidant, phase II and III responses induced by lipoic acid in the fish Jenynsia Multidentata (Anablapidae) and its influence on endolsulfan accumulation and toxicity, Pesticide Biochem. Physiol. **2014,** 108, 8–15, doi.org/10.1016/j.pestbp.2013.10.009.

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

60. Piechota-Polanczyk, A., Zielińska, M., and Fichna, J. The influence of lipoic acid on caveolin-1-regulated antioxidative enzymes in the mouse model of acute ulcerative colitis, Biomed. Pharmacother. **2016,** 84, 470-475, doi.org/10.1016/j.biopha.2016.09.066.

61. Bhattacharyya, A., Chattopadhyay, R., and Crowe, S. E. Oxidative stress: an essential factor in the pathogenesis of gastrointestinal mucosal diseases, Physiol. Rev. **2014,** 94, 329-354, doi.org/10.1152/physrev.00040.2012.

62. Packer, L., Kraemer, K., and Rimbach, G. Molecular aspects of lipoic acid in the prevention of diabetes complications, Nutrition **2001,** 17, 888-895, doi.org/10.1016/S0899-9007(01)00658-X.

63. Sezgin, A., Altuntaş, C., Demiralay, M., and Terzi, R. Exogenous alpha lipoic acid can stimulate photosystem II activity and the gene expressions of carbon fixation and chlorophyll metabolism enzymes in maize seedlings under drought, J. Plant Physiol. **2019,** 232, 65–73, doi.org/10.1016/j.jplph.2018.11.026.

64. Biewenga, G. P., Dorstijn, M. A., Verhagen, J. V., and Bast, A. Reduction of lipoic acid by lipoamide dehydrogenase, Biochem. Pharmacol. **1996,** 51, 233-238, doi.org/10.1016/0006-2952(95)02124-8.

65. Tan, W., Zhang, J., Mi, Y., and Guo, Z. Synthesis and characterization of α-lipoic acid grafted chitosan derivatives with antioxidant activity, React. Funct. Polym. **2022,** 172, 105205, doi.org/10.1016/j.reactfunctpolym.2022.105205.

66. El Basuini, M. F., Shahin, S. A., Eldenary, M. E., Elshora, S. M., and Mourad, M. M. Growth variables, feed efficacy, survival rate, and antioxidant capacity of european seabass (Dicentrarchus Labrax l.) larvae treated with coenzyme Q10 or lipoic acid, Aquac. Rep. **2022,** 27, 101373, doi.org/10.1016/j.aqrep.2022.101373.

67. Huang, C., Sun, J., Ji, H., Oku, H., Chang, Z., and Xie, J. Influence of dietary alpha-lipoic acid and lipid level on the growth performance, food intake and gene expression of peripheral appetite regulating factors in juvenile grass carp (Ctenopharyngodon Idellus), Aquaculture **2019,** 505, 412–422,

doi.org/10.1016/j.aquaculture.2019.02.054.

68. Biewenga, G. P., and Bast, A. The pharmacology of the antioxidant: lipoic acid, Gen. Pharmacol. **1997,** 29, 315-331, doi.org/10.1016/S0306-3623(96)00474-0.

69. Lopez-Maldonado, A., Pastoriza, S., and Rufián-Henares, J. Á. Assessing the antioxidant and metabolic effect of an alpha-lipoic acid and acetyl-L-carnitine nutraceutical, Curr. Res. Food Sci. **2021,** 4, 336-344, doi.org/10.1016/j.crfs.2021.05.002.

70. Singer, A. J., and Clark, R. A. F. Cutaneous wound healing, N. Engl. J. Med. **1999,** 341, 738–746, doi.org/10.1056/NEJM199909023411006.

71. Leu, J.G., Chen, S.A., Chen, H.M., Wu, W.M., Hung, C.F., and Liang, Y.J. The effects of gold nanoparticles in wound healing with antioxidant epigallocatechin gallate and α-lipoic acid, Nanomedicine **2012,** 8, 767–775, doi.org/10.1016/j.nano.2011.08.013.

72. Alleva, R., Tomasetti, M., Sartini, D., Emanuelli, M., Nasole, E., and Neuzil, J. α-Lipoic acid modulates extracellular matrix and angiogenesis gene expression in non-healing wounds treated with hyperbaric oxygen therapy, Mol. Med. **2008,** 14, 175-183, doi.org/10.2119/2007-00095.Alleva.

73. Salinthone, S., Schillace, R. V., Marracci, G. H., and Carr, D. W. Lipoic acid stimulates cAMP production via the EP2 and EP4 prostanoid receptors and inhibits IFN gamma synthesis and cellular cytotoxicity in NK cells, J. Neuroimmunol. **2008,** 199, 46-55, doi.org/10.1016/j.jneuroim.2008.05.003.

74. Tanaka, Y., Kaibori, M., Miki, H., Nakatake, R., Tokuhara, K., and Kwon, A. H. Alpha-lipoic acid exerts a liver-protective effect in acute liver injury rats, J. Surg. Res. **2015,** 193, 675-683, doi.org/10.1016/j.jss.2014.08.057.

75. Mor, G., Cardenas, I., Abrahams, V., and Guller, S. Inflammation and pregnancy: the role of the immune system at the implantation site, Ann. N. Y. Acad. Sci. **2011,** 1221, 80-87, doi.org/10.1111/j.1749-6632.2010.05938.x.

76. Bao, P., Kodra, A., Tomic-Canic, M., Golinko, M. S., and Brem, H. The role of vascular endothelial growth factor in wound healing, J. Surg. Res. **2009,** 153, 347-358, doi.org/10.1016/j.jss.2008.04.023.

77. Gorąca, A., Piechota, A., Kleniewska, P., and Skibska, B. Lipoic acid - biological activity and therapeutic potential, Pharmacol. Rep. **2011,** 63, 849-858, doi.org/10.1016/S1734-1140(11)70600-4.

78. Collins, T., and Maniatis, T. Transcriptional regulation of endothelial cell adhesion molecules: NF-kappa B and cytokine-inducible enhancers, FASEB J. **1995,** 9, 899-909, doi.org/10.1096/fasebj.9.10.7542214.

79. Zhang, W. J., and Frei, B. α-lipoic acid inhibits TNF-a-induced NF-κB activation and adhesion molecule expression in human aortic endothelial cells, FASEB J. **2001,** 15, 2423-2432, doi.org/10.1096/fj.01-0260com.

80. Weber, C., Erl, W., Pietsch, A., and Weber, P. C. Aspirin inhibits nuclear factor-κB mobilization and monocyte adhesion in stimulated human endothelial cells, Circulation **1995,** 91, 1914-1917, doi.org/10.1161/01.CIR.91.7.1914.

81. Albelda, S. M., Smith, C. W., and Ward, P. A. Adhesion molecules and inflammatory injury, FASEB J. **1994,** 8, 504-512, doi.org/10.1096/fasebj.8.8.8181668.

82. Yadav, V., Marracci, G., Lovera, J., Woodward, W., Bogardus, K., and Bourdette, D. N. Lipoic acid in multiple sclerosis: a pilot study, Multiple Sclerosis **2005,** 11, 159-165, doi.org/10.1191/1352458505ms1143oa.

83. Ziegler, Dan. Thioctic acid for patients with symptomatic diabetic polyneuropathy: a critical review, Treat. Endocrinol. **2004,** 3, 173-189, doi.org/10.2165/00024677-200403030-00005.

84. Melhem, A., Stern, M., Shibolet, O., Israeli, E., Ackerman, Z., and Ilan, Y. Treatment of chronic hepatitis C virus infection via antioxidants, J. Clin. Gastroenterol. **2005,** 39, 737–742, doi.org/10.1097/01.mcg.0000174023.73472.29.

85. Jesudason, E. P., Masilamoni, J. G., and Jayakumar, R. The protective role of DL- α -lipoic acid in the oxidative vulnerability triggered by A ß -amyloid vaccination in mice, Mol. Cell. Biochem. **2005,** 270, 29–37, doi.org/10.1007/s11010-005-3301-z.

86. Guha, M., and Mackman, N. The phosphatidylinositol 3-kinase-akt pathway limits lipopolysaccharide activation of signaling pathways and expression of inflammatory mediators in human monocytic cells, J. Biol. Chem. **2002,** 277, 32124–32132, doi.org/10.1074/jbc.M203298200.

87. Fukao, T., and Koyasu, S. PI3K and negative regulation of TLR signaling, Trends Immunol. **2003,** 24, 358–363, doi.org/10.1016/S1471-4906(03)00139-X.

88. Alhakamy, N. A., Al-Rabia, M. W., Asfour, H. Z., Alshehri, S., Alharbi, W. S., and Kotta, S. 2-Methoxy-estradiol loaded alpha lipoic acid nanoparticles augment cytotoxicity in MCF-7 breast cancer cells, Dose-Response **2021,** 19, 15593258211055023, doi.org/10.1177/15593258211055023.

89. Campoccia, D., Montanaro, L., and Arciola, C. R. The significance of infection related to orthopedic devices and issues of antibiotic resistance, Biomaterials **2006,** 27, 2331-2339¸ doi.org/10.1016/j.biomaterials.2005.11.044.

90. Choi, M. J., Kim, S. A., and Rhee, M. S. New decontamination method based on caprylic acid in combination with citric acid or vanillin for eliminating Cronobacter Sakazakii and Salmonella Enterica serovar typhimurium in reconstituted infant formula, Int. J. Food Microbiol. **2013,** 166, 499-507, doi.org/10.1016/j.ijfoodmicro.2013.08.016.

91. Abdelmoneim, D., Porter, G., Duncan, W., Lim, K., Easingwood, R., and Coates, D. Three-dimensional evaluation of the cytotoxicity and antibacterial properties of alpha lipoic acid-capped silver nanoparticle constructs for oral applications, Nanomaterials **2023,** 13, 705, doi.org/10.3390/nano13040705.

92. Iversen, C., Waddington, M., and Forsythe, S. Identification and phylogeny of Enterobacter Sakazakii relative to Enterobacter and Citrobacter species, J. Clin. Microbiol. **2004,** 42, 5368-5370, doi.org/10.1128/JCM.42.11.5368-5370.2004.

93. Hajtuch, J., Wojcik, M., Tomczyk, E., Jaskiewicz, M., and Inkielewicz-Stepniak, I. Lipoic acid-coated silver nanoparticles: biosafety potential on the vascular microenvironment and antibacterial properties, Front. Pharmacol. **2022,** 12, 733743, doi.org/10.3389/fphar.2021.733743.

94. Martínez, G. K. D., Zertuche, A. T., Iñiguez, E., and Kretzchmar, T. Radical scavenging, hemocompatibility, and antibacterial activity against MDR acinetobacter baumannii in alginate-based aerogels containing lipoic acid-capped silver nanoparticles, ACS Omega **2024,** 9, 2350-2361, doi.org/10.1021/acsomega.3c06114.

95. Wright, E. J., Brew, B. J., and Wesselingh, S. L. Pathogenesis and diagnosis of viral infections of the nervous system, Neurol. Clin. **2008,** 26, 617-633, doi.org/10.1016/j.ncl.2008.03.006.

96. Cure, E., and Cumhur Cure, M. Alpha-lipoic acid may protect patients with diabetes against COVID-19 infection, Med. Hypotheses **2020,** 143, 110185, doi.org/10.1016/j.mehy.2020.110185.

97. Koufaki, M., Detsi, A., and Kiziridi, C. Multifunctional lipoic acid conjugates, Curr. Med. Chem. **2009,** 16, 4728-4742, doi.org/10.2174/092986709789878274.

98. Spisakova, M., Cizek, Z., and Melkova, Z. Ethacrynic and α-lipoic acids inhibit vaccinia virus late gene expression, Antiviral Res. **2009,** 81, 156–165, doi.org/10.1016/j.antiviral.2008.11.001.

99. Zhang, W., Chen, X., Yu, F., Li, F., Li, W., and Jia, K. α-lipoic acid exerts its antiviral effect against viral hemorrhagic septicemia virus (VHSV) by promoting upregulation of antiviral genes and suppressing VHSV-induced oxidative stress, Virol. Sin. **2021,** 36, 1520–1531, doi.org/10.1007/s12250-021-00440-5.

100. Baur, A., Harrer, T., Peukert, M., Jahn, G., and Fleckenstein, B. Alpha-lipoic acid is an effective inhibitor of human immuno-deficiency virus (HIV-1) replication, Klin. Wochenschrift **1991,** 69, 722-724, doi.org/10.1007/BF01649442.

101. Ray, P. D., Huang, B.W., and Tsuji, Y. Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling, Cell. Signal. **2012,** 24, 981–990, doi.org/10.1016/j.cellsig.2012.01.008.

102. Huang, W.J., Zhang, X., and Chen, W.W. Role of oxidative stress in Alzheimer's disease, Biomed. Rep. **2016,** 4, 519–522, doi.org/10.3892/br.2016.630.

103. Iqbal, K., and Grundke-Iqbal, I. Alzheimer neurofibrillary degeneration: significance, etiopathogenesis, therapeutics and prevention: Alzheimer review series, J. Cell. Mol. Med. **2008,** 12, 38-55, doi.org/10.1111/j.1582-4934.2008.00225.x.

104. Rubio-Perez, J. M., and Morillas-Ruiz, J. M. (2012) A review: inflammatory process in Alzheimer's disease, role of cytokines, Sci. World J. **2012,** 756357, doi.org/10.1100/2012/756357.

105. Sano, M., Ernesto, C., Thomas, R. G., Klauber, M. R., Schafer, K., and Thal, L. J. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease, N. Engl. J. Med. **1997,** 336, 1216-1222, doi.org/10.1056/nejm199704243361704.

106. Dinicola, S., Proietti, S., Cucina, A., Bizzarri, M., and Fuso, A. Alpha-lipoic acid downregulates IL-1ß and IL-6 by DNA hypermethylation in SK-N-BE neuroblastoma cells, Antioxidants **2017,** 6, 74, doi.org/10.3390/antiox6040074.

107. Jia, Z., Hallur, S., Zhu, H., Li, Y., and Misra, H. P. Potent upregulation of glutathione and NAD(P)H: quinone oxidoreductase 1 by alpha-lipoic acid in human neuroblastoma SH-SY5Y cells: protection against neurotoxicant-elicited cytotoxicity, Neurochem. Res. **2008,** 33, 790-800, doi.org/10.1007/s11064-007-9496-5.

108. Cacciatore, I., Marinelli, L., Fornasari, E., Cerasa, L. S., and Eusepi, P. Novel NSAID-derived drugs for the potential treatment of Alzheimer's disease, Int. J. Mol. Sci. **2016,** 17, 1035, doi.org/10.3390/ijms17071035.

109. Allahverdiyev, O., Dzhafar, S., Berköz, M., and Yıldırım, M. Advances in current medication and new therapeutic approaches in epilepsy, Eastern J. Med. **2018,** 23, 48-59, doi.org/10.5505/ejm.2018.62534.

110. Büget, B., Türkmen, A. Z., Allahverdiyev, O., and Enginar, N. Antimuscarinic-induced convulsions in fasted animals after food intake: evaluation of the effects of levetiracetam, topiramate and different doses of atropine, Naunyn-Schmiedebergs Arch. Pharmacol. **2016,** 389, 57–62, doi.org/10.1007/s00210-015-1175-5.

111. Martinc, B., Grabnar, I., and Vovk, T. The role of reactive species in epileptogenesis and influence of antiepileptic drug therapy on oxidative stress, Curr. Neuropharmacol. **2012,** 10, 328-343, doi.org/10.2174/157015912804143504.

112. Javaid, M. S., Antonic-Baker, A., Pitsillou, E., Liang, J., French, C., and Anderson, A. Alpha-lipoic acid analogues in the regulation of redox balance in epilepsy: a molecular docking and simulation study, J. Mol. Graph. Model. **2022,** 112, 108116, doi.org/10.1016/j.jmgm.2021.108116.

113. Sagmanligil, H., Yunusoglu, O., and Catalkaya, E. Investigation of the pharmacological, behavioral and biochemical effects of boron on rats with rotenone-induced Parkinson's disease, Cell. Mol. Biol. **2022,** 68, 13–21, doi.org/10.14715/cmb/2022.68.8.3.

114. Kaygısız, M., & Gürer, E. S. Determination of the antimicrobial, antioxidant activities and effects on oxidative DNA damage of extracts from three different Salvia species grown in Turkey. Prospects in Pharmaceutical Sciences **2025,** 23(1), 1-8. doi.org/10.56782/pps.300

115. Xicoy, H., Wieringa, B., and Martens, G. J. M. The role of lipids in Parkinson's disease, Cells **2019,** 8, 1–58, doi.org/10.3390/cells8010027.

116. Zheng, Q., Ma, P., Yang, P., Zhai, S., He, M., and Zhang, C. Alpha lipoic acid ameliorates motor deficits by inhibiting ferroptosis in Parkinson's disease, Neurosci. Lett. **2023,** 810, 137346, doi.org/10.1016/j.neulet.2023.137346.

117. Piersimoni, M. E., Teng, X., and Ying, L. Antioxidant lipoic acid ligand-shell gold nanoconjugates against oxidative stress caused by α-synuclein aggregates, Nanoscale Adv. **2020,** 2, 5666–5681, doi.org/10.1039/D0NA00688B.

118. Tai, S., Zheng, Q., Zhai, S., Cai, T., Xu, L., and Zhang, C. Alpha-lipoic acid mediates clearance of iron accumulation by regulating iron metabolism in a Parkinson's disease model induced by 6-OHDA, Front. Neurosci. **2020,** 14, 612, doi.org/10.3389/fnins.2020.00612.

119. Li, X., Zou, Y., Xing, J., Wang, K. Y., and Zhai, X. Y. A-lipoic acid alleviates folic acid-induced renal damage through inhibition of ferroptosis, Front. Physiol. **2021,** 12, 680544, doi.org/10.3389/fphys.2021.680544.

120. Abdin, A. A., and Sarhan, N. I. Intervention of mitochondrial dysfunction-oxidative stress-dependent apoptosis as a possible neuroprotective mechanism of α-lipoic acid against rotenone-induced parkinsonism and l-dopa toxicity, Neurosci. Res. **2011,** 71, 387–39, doi.org/10.1016/j.neures.2011.08.008.

121. Pei, X., Hu, F., Hu, Z., Luo, F., Li, X., and Long, D. Neuroprotective effect of α-lipoic acid against Aβ25–35-induced damage in BV2 cells, Molecules **2023,** 28, 1–13, doi.org/10.3390/molecules28031168.

122. Sahin, M., Sagdıc, G., Elmas, O., Akpınar, D., Derin, N., and Yargıcoğlu, P. Effect of chronic restraint stress and alpha-lipoic acid on lipid peroxidation and antioxidant enzyme activities in rat peripheral organs, Pharmacol. Res. **2006,** 54, 247–252, doi.org/10.1016/j.phrs.2006.05.007.

123. Liu, J., Wang, X., and Mori, A. Immobilization stress-induced antioxidant defense changes in rat plasma: effect of treatment with reduced glutathione, Int. J. Biochem. **1994,** 26, 511-517, doi.org/10.1016/0020-711X(94)90008-6.

124. Akotkar, L., Aswar, U., Patil, R., Kumar, D., Aswar, M., and Gurav, S. Antidepressant effect of alpha lipoic acid in rats exposed to chronic unpredictable mild stress: putative role of neurotransmitters and 5HT3 receptor, Future Pharmacol. **2023,** 3, 407–425, doi.org/10.3390/futurepharmacol3020025.

125. Sampaio, L. R. L., Cysne Filho, F. M. S., and Vasconcelos, S. M. M. Advantages of the alpha-lipoic acid association with chlorpromazine in a model of schizophrenia induced by ketamine in rats: behavioral and oxidative stress evidences, Neuroscience **2018,** 373, 72–81, doi.org/10.1016/j.neuroscience.2018.01.008.

126. Mansur, R. B., Cha, D. S., Asevedo, E., and Brietzke, E. Selfish brain and neuroprogression in bipolar disorder, Prog. Neuropsychopharmacol. Biol. Psychiatry **2013,** 43, 66-71, doi.org/10.1016/j.pnpbp.2012.12.004.

127. Kim, M. S., Park, J. Y., Namkoong, C., Jang, P. G., Ryu, J. W., and Lee, K. U. Anti-obesity effects of α-lipoic acid mediated by suppression of hypothalamic AMP-activated protein kinase, Nat. Med. **2004,** 10, 727-733, doi.org/10.1038/nm1061.

128. Kim, E., Park, D. W., Choi, S. H., and Cho, H. S. A preliminary investigation of α-lipoic acid treatment of antipsychotic drug-induced weight gain in patients with schizophrenia, J. Clin. Psychopharmacol. **2008,** 28, 138-146, doi.org/10.1097/JCP.0b013e31816777f7.

129. Sampaio, L. R. L., Borges, L. T. N., Barbosa, T. M., Matos, N. C. B., Lima, R. de F., and Vasconcelos, S. M. M. de. Electroencephalographic study of chlorpromazine alone or combined with alpha-lipoic acid in a model of schizophrenia induced by ketamine in rats, J. Psychiatr. Res. **2017,** 86, 73–82, doi.org/10.1016/j.jpsychires.2016.12.003.

130. Farr, S. A., Poon, H. F., Drake, J., Banks, W. A., and Morley, J. E. The antioxidants α-lipoic acid and N -acetylcysteine reverse memory impairment and brain oxidative stress in aged SAMP8 mice, J. Neurochemi. **2003,** 84, 1173–1183, doi.org/10.1046/j.1471-4159.2003.01580.x.

131. Memudu, A. E., and Adanike, R. P. Alpha lipoic acid reverses scopolamine-induced spatial memory loss and pyramidal cell neurodegeneration in the prefrontal cortex of wistar rats, IBRO Neurosci. Rep. **2022,** 13, 1–8, doi.org/10.1016/j.ibneur.2022.05.005.

132. Liu, B., Ma, X., Guo, D., Guo, Y., and Bi, H. Neuroprotective effect of alpha-lipoic acid on hydrostatic pressure-induced damage of retinal ganglion cells in vitro, Neurosci. Lett. **2012,** 526, 24–28, doi.org/10.1016/j.neulet.2012.08.016.

133. Han, D., Sen, C. K., Roy, S., Kobayashi, M. S., and Packer, L. Protection against glutamate-induced cytotoxicity in C6 glial cells by thiol antioxidants, Am. J. Physiol. Regul. Integr. Comp. Physiol. **1997,** 273, 1771–1778, doi.org/10.1152/ajpregu.1997.273.5.R1771.

134. Sun, H., Yao, W., Tang, Y., Zhuang, W., Wu, D., and Sheng, H. Urinary exosomes as a novel biomarker for evaluation of α-lipoic acid's protective effect in early diabetic nephropathy, J. Clin. Lab. Anal. **2017,** 31, e22129, doi.org/10.1002/jcla.22129.

135. Lin, H., Ye, S., Xu, J., and Wang, W. The alpha-lipoic acid decreases urinary podocalyxin excretion in type 2 diabetics by inhibiting oxidative stress in vivo, J. Diabetes Complications **2015,** 29, 64–67, doi.org/10.1016/j.jdiacomp.2014.09.011.

136. Wang, L., Tang, Y., Eisner, W., Sparks, M. A., and Spurney, R. F. Augmenting podocyte injury promotes advanced diabetic kidney disease in Akita mice, Biochem. Bioph Res. Commun. **2014,** 444, 622-627, doi.org/10.1016/j.bbrc.2014.01.115.

137. Gui, D., Guo, Y., Wang, F., Liu, W., Chen, J., and Wang, N. Astragaloside IV, a novel antioxidant, prevents glucose-induced podocyte apoptosis in vitro and in vivo, PLoS One **2012,** 7, e39824, doi.org/10.1371/journal.pone.0039824.

138. Jacob, S., Streeper, R. S., Fogt, D. L., Hokama, J. Y., Tritschler, H. J., and Henriksen, E. J. The antioxidant α-lipoic acid enhances insulin-stimulated glucose metabolism in insulin-resistant rat skeletal muscle, Diabetes **1996,** 45, 1024-1029, doi.org/10.2337/diabetes.45.8.1024.

139. Khamaisi, M., Potashnik, R., Tirosh, A., Demshchak, E., Rudich, A., and Bashan, N. Lipoic acid reduces glycemia and increases muscle GLUT4 content in streptozotocin-diabetic rats, Metabolism **1997,** 46, 763-768, doi.org/10.1016/S0026-0495(97)90120-7.

140. Nagamatsu, M., Nickander, K. K., Schmelzer, J. D., Raya, A., Wittrock, D. A., and Low, P. A. Lipoic acid improves nerve blood flow, reduces oxidative stress, and improves distal nerve conduction in experimental diabetic neuropathy, Diabetes Care **1995,** 18, 1160-

1167, doi.org/10.2337/diacare.18.8.1160.

141. Papanas, N., and Ziegler, D. Efficacy of α-lipoic acid in diabetic neuropathy, Expert Opin. Pharmacother. **2014,** 15, 2721–2731, doi.org/10.1517/14656566.2014.972935.

142. Jain, S. K., and Lim, G. Lipoic acid decreases lipid peroxidation and protein glycosylation and increases (Na+ + K+) and Ca++ATPase activities in high glucose-treated human erythrocytes, Free Radic. Biol. Med. **2000,** 29, 1122-1128, doi.org/10.1016/S0891-5849(00)00410-X.

143. Ziegler, D., Hanefeld, M., Ruhnau, K. J., Hasche, H., Lobisch, M., and Malessa, R. Treatment of symptomatic diabetic polyneuropathy with the antioxidant α-lipoic acid: a 7-month multicenter randomized controlled trial (ALADIN III study), Diabetes Care **1999,** 22, 1296-1301, doi.org/10.2337/diacare.22.8.1296.

144. Mervaala, E., Finckenberg, P., Lapatto, R., Müller, D. N., Park, J. K., and Luft, F. C. Lipoic acid supplementation prevents angiotensin II-induced renal injury, Kidney Int. **2003,** 64, 501-508, doi.org/10.1046/j.1523-1755.2003.00108.x.

145. Melhem, M. F., Craven, P. A., and DeRubertis, F. R. Effects of dietary supplementation of α-lipoic acid on early glomerular injury in diabetes mellitus, J. Am. Soc. Nephrol. **2001,** 12, 124-133, doi.org/10.1681/asn.v121124.

146. Dinçer, Y., Telci, A., Kayali, R., Yilmaz, I. A., and Akçay, T. Effect of α-lipoic acid on lipid peroxidation and anti-oxidant enzyme activities in diabetic rats, Clin. Exp. Pharmacol. Physiol. **2002,** 29, 281-284, doi.org/10.1046/j.1440-1681.2002.03642.x.

147.Maritim, A. C., Sanders, R. A., and Watkins, J. B. Effects of α-lipoic acid on biomarkers of oxidative stress in streptozotocin-induced diabetic rats, J. Nutr. Biochem. **2003,** 14, 288-294, doi.org/10.1016/S0955-2863(03)00036-6.

148. Bhatti, F., Mankhey, R. W., Asico, L., Quinn, M. T., and Maric, C. Mechanisms of antioxidant and pro-oxidant effects of α-lipoic acid in the diabetic and nondiabetic kidney, Kidney Int. **2005,** 67, 1371-1380, doi.org/10.1111/j.1523-1755.2005.00214.x.

149. Manaviat M., Rashidi M., and Shoja RM. Prevalence of dry eye syndrome and diabetic retinopathy in type 2 diabetic patients, BMC Ophthalmol. **2008,** 8, 1-5, doi.org/10.1186/1471-2415-8-10.

150. Alvarez-Rivera F., Fernández-Villanueva D., and Concheiro A. α-Lipoic acid in Soluplus(®) polymeric nanomicelles for ocular treatment of diabetes-associated corneal diseases, J. Pharm. Sci. **2016,** 105, 2855–2863, doi.org/10.1016/j.xphs.2016.03.006.

151. Pawankar, R. Allergic diseases and asthma: a global public health concern and a call to action, World Allergy Organization **2014,** 7, 1-3, doi.org/10.1186/1939-4551-7-12.

152. Druce, H. M. Allergic Rhinitis, JAMA **1988,** 259, 260, doi.org/10.1001/jama.1988.03720020062038.

153. Choi, Y. H., Chai, O. H., Han, E.H., Choi, S.Y., and Song, C. H. Lipoic acid suppresses compound 48/80-induced anaphylaxis-like reaction, Anat. Cell Biol. **2010,** 43, 317, doi.org/10.5115/acb.2010.43.4.317.

154. Small, P., and Kim, H. Allergic rhinitis, Allergy, Asthma Clin. Immunol. **2011,** 7, 1-8, doi.org/10.1186/1710-1492-7-S1-S3.

155. Van Nguyen, T., Piao, C. H., Fan, Y. J., Shin, D. U., Kim, S. Y., and Chai, O. H. Anti-allergic rhinitis activity of α-lipoic acid via balancing Th17/Treg expression and enhancing Nrf2/HO-1 pathway signaling, Sci. Rep. **2020,** 10, 12528, doi.org/10.1038/s41598-020-69234-1.

156. Zhao, H., Zhao, X., Liu, L., Zhang, H., Xuan, M., and Liu, C. Neurochemical effects of the R form of α-lipoic acid and its neuroprotective mechanism in cellular models of Parkinson's disease, Int. J. Biochem. Cell Biol. **2017,** 87, 86–94, doi.org/10.1016/j.biocel.2017.04.002.

157. Sen, C. K., Roy, S., and Packer, L. Fas mediated apoptosis of human jurkat T-cells: intracellular events and potentiation by redox-active α-lipoic acid, Cell Death Differ. **1999,** 6, 481-491, doi.org/10.1038/sj.cdd.4400514.

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

159. Schwartz, L., Abolhassani, M., Guais, A., Sanders, E., and Campion, F. A combination of alpha lipoic acid and calcium hydroxycitrate is efficient against mouse cancer models: preliminary results, Oncol. Rep. **2010,** 23, 1407-1416, doi.org/10.3892/or_00000778.

160. Ahmadi, A., Hosseini, F., and Soukhtanloo, M. Anticancer effects of alpha-lipoic acid, a potent organosulfur compound by modulating matrix metalloproteinases and apoptotic markers in osteosarcoma MG-63 cells, J. Steroid Biochem. Mol. Biol. **2025,** 247, 106664, doi.org/10.1016/j.jsbmb.2024.106664.

161. Jeon, M. J., Kim, W. G., Lim, S., Choi, H.J., Sim, S., and Kim, W. B. Alpha lipoic acid inhibits proliferation and epithelial mesenchymal transition of thyroid cancer cells, Mol. Cell. Endocrinol. **2016,** 419, 113–123, doi.org/10.1016/j.mce.2015.10.005.

162.Na, M. H., Seo, E. Y., and Kim, W. K.Effects of α-lipoic acid on cell proliferation and apoptosis in MDA-MB-231 human breast cells, Nutr. Res. Pract. **2009,** 3, 265, doi.org/10.4162/nrp.2009.3.4.265.

163. Kuban-Jankowska, A., Gorska-Ponikowska, M., and Wozniak, M. Lipoic acid decreases the viability of breast cancer cells and activity of PTP1B and SHP2, Anticancer Res. **2017,** 37, 2893-2898, doi.org/10.21873/anticanres.11642.

164. Zhang, W. J., Wei, H., and Frei, B. α-Lipoic acid attenuates LPS-induced inflammatory responses by activating the phosphoinositide 3-kinase/Akt signaling pathway, Proc. Natl. Acad. Sci. **2007,** 104, 4077–4082, doi.org/10.1073/pnas.0700305104.

165. Faverani, L. P., Polo, T. O. B., Ramalho-Ferreira, G., Momesso, G. A. C., Hassumi, J. S., Rossi, A. C., ... & Okamoto, R. Raloxifene but not alendronate can compensate the impaired osseointegration in osteoporotic rats. Clinical oral investigations **2018,** 22, 255-265.

166. Koh, J. M., Lee, Y. S., Byun, C. H., Chang, E. J., Kim, H., and Kim, G. S. α-Lipoic acid suppresses osteoclastogenesis despite increasing the receptor activator of nuclear factor κB ligand/osteoprotegerin ratio in human bone marrow stromal cells, J. Endocrinol. **2005,** 185, 401-413, doi.org/10.1677/joe.1.05995.

167. Lin, Z., Guichun, Z., Lifeng, L., Chen, C., and Jinfang, C. Protective effect of α-lipoic acid against antimycin a cytotoxicity in MC3T3-E1 osteoblastic cells, Cell Stress Chaperones **2017,** 22, 5–13, doi.org/10.1007/s12192-016-0735-z.

168. Cheng, M., Wang, Q., Fan, Y., Liu, X., Wang, L., and Sun, W. A traditional Chinese herbal preparation, er-zhi-wan, prevent ovariectomy-induced osteoporosis in rats, J. Ethnopharmacol. **2011,** 138, 279–285, doi.org/10.1016/j.jep.2011.09.030.

169. Vivanco, I., and Sawyers, C. L. The phosphatidylinositol 3-kinase–AKT pathway in human cancer, Nat. Rev. Cancer **2002,** 2, 489–501, doi.org/10.1038/nrc839.

170. Fu, C., Xu, D., Wang, C. Y., Jin, Y., Liu, Q., and Liu, M. Z. Alpha-lipoic acid promotes osteoblastic formation in H2O2-treated MC3T3-E1 cells and prevents bone loss in ovariectomized rats, J. Cell. Physiol. **2015,** 230, 2184-2201, doi.org/10.1002/jcp.24947.

171. Xiao, Y., Cui, J., and Le, G. Lipoic acid increases the expression of genes involved in bone formation in mice fed a high-fat diet, Nutrition Research **2011,** 31, 309–317, doi.org/10.1016/j.nutres.2011.03.013.

172. Abdelhalim, M. A. K., Qaid, H. A. Y., and Ghannam, M. M. The protective roles of vitamin E and α-lipoic acid against nephrotoxicity, lipid peroxidation, and inflammatory damage induced by gold nanoparticles, Int. J. Nanomedicine **2020,** 15, 729–734, doi.org/10.2147/IJN.S192740.

173. Ossipov, D. A. Bisphosphonate-modified biomaterials for drug delivery and bone tissue engineering, Expert Opin. Drug Deliv. **2015,** 12, 1443–1458, doi.org/10.1517/17425247.2015.1021679.

174. Gao, W., Li, J. J., Shi, J., Lan, H., and Fu, D. Ångstrom-scale gold particles loaded with alendronate via alpha-lipoic acid alleviate bone loss in osteoporotic mice, J. Nanobiotechnology **2024,** 22, 212, doi.org/10.1186/s12951-024-02466-9.

175. Lu, S.Y., Wang, C.Y., Jin, Y., Meng, Q., Liu, Q., and Liu, M.Z. The osteogenesis-promoting effects of alpha-lipoic acid against glucocorticoid-induced osteoporosis through the NOX4, NF-kappaB, JNK and PI3K/AKT pathways, Sci. Rep. **2017,** 7, 3331, doi.org/10.1038/s41598-017-03187-w.

176. Wollin, S. D., Wang, Y., and Jones, P. J. H. Effects of a medium chain triglyceride oil mixture and α-lipoic acid diet on body composition, antioxidant status, and plasma lipid levels in the golden syrian hamster, J. Nutr. Biochem. **2004,** 15, 402–410, doi.org/10.1016/j.jnutbio.2003.12.001.

177. Bai, J., Chen, C., Sun, Y., Li, S., He, R., and Han, Z. α-LA attenuates microcystin-LR-induced hepatocellular oxidative stress in mice through Nrf2-mediated antioxidant and detoxifying enzymes, Toxicon **2023,** 235, 107313, doi.org/10.1016/j.toxicon.2023.107313.

178. Zhang, L., Zou, J., Chai, E., and Zhang, Y. Alpha-lipoic acid attenuates cardiac hypertrophy via downregulation of PARP-2 and subsequent activation of SIRT-1, Eur. J. Pharmacol. **2014,** 744, 203–210, doi.org/10.1016/j.ejphar.2014.09.037.

179. Quinn, M. T., Parthasarathy, S., and Steinberg, D. Oxidatively modified low density lipoproteins: a potential role in recruitment and retention of monocyte/macrophages during atherogenesis, Proc. Natl. Acad. Sci. U. S. A. **1987,** 84, 2995-2998, doi.org/10.1073/pnas.84.9.2995.

180. Meneses, L. N., Vasconcelos, G. S., Da Silva Medeiros, I., Silva, M. C. C., and Vasconcelos, S. M. M. Neuroprotective evidence of alpha-lipoic acid and desvenlafaxine on memory deficit in a neuroendocrine model of depression, Naunyn Schmiedebergs Arch. Pharmacol. **2018,** 391, 803-817, doi.org/10.1007/s00210-018-1509-1.

181. Berköz, M., Aslan, A., Yunusoğlu, O., and Francik, R. Hepatoprotective potentials of Usnea Longissima Ach. and Xanthoparmelia Somloensis (gyelnik) hale extracts in ethanol-induced liver injury, Drug Chem. Toxicol. **2025,** 48, 136–149, doi.org/10.1080/01480545.2024.2407867.

182. Ceylanlı, D., Şehirli, A. Ö., Gençosman, S., Teralı, K., Şah, H., and Sayıner, S. Protective effects of alpha-lipoic acid against 5-fluorouracil-induced gastrointestinal mucositis in rats, Antioxidants **2022,** 11, 1930, doi.org/10.3390/antiox11101930.

183. Babu, S., Manoharan, S., and Perumal, E. Role of oxidative stress-mediated cell death and signaling pathways in experimental fluorosis, Chem. Biol. Interact. **2022,** 365, 110106, doi.org/10.1016/j.cbi.2022.110106.

184. Elshazly, S. M., El-Moselhy, M. A., and Barakat, W. Insights in the mechanism underlying the protective effect of α-lipoic acid against acetaminophen-hepatotoxicity, Eur. J. Pharmacol. **2014,** 726, 116–123, doi.org/10.1016/j.ejphar.2014.01.042.

185. Keith, D. J., Butler, J. A., Bemer, B., Dixon, B., Johnson, S., and Hagen, T. M. Age and gender dependent bioavailability of R- and S-α-lipoic acid: a pilot study, Pharmacol. Res. **2012,** 66, 199-206, doi.org/10.1016/j.phrs.2012.05.002.

186. Guzel, E. E., Kaya, N., Ozan, G., Tektemur, A., and Ozan, I. E. The investigation of effect of alpha lipoic acid against damage on neonatal rat lung to maternal tobacco smoke exposure, Toxicol. Rep. **2018,** 5, 714-722, doi.org/10.1016/j.toxrep.2018.05.014.

187. Yunusoglu, O., Türkmen, Ö., Berkoz, M., and Yalın, S. In vitro anti-obesity effect of aloe vera extract through transcription factors and lipolysis-associated genes, Eastern J. Med. **2022,** 27, 519–528, doi.org/10.5505/ejm.2022.13285.

188. Romo-Hualde, A., Huerta, A. E., González-Navarro, C. J., Ramos-López, O., and Martínez, J. A. Untargeted metabolomic on urine samples after α-lipoic acid and/or eicosapentaenoic acid supplementation in healthy overweight/obese women, Lipids Health Dis. **2018,** 17, 1-13, doi.org/10.1186/s12944-018-0750-4.

189. Namazi, N., Larijani, B., and Azadbakht, L. Alpha-lipoic

acid supplement in obesity treatment: a systematic review and meta-analysis of clinical trials, Clinical Nutrition **2018,** 37, 419–428, doi.org/10.1016/j.clnu.2017.06.002.

190. Dajnowicz-Brzezik, P., Żebrowska, E., Maciejczyk, M., and Chabowski, A. The effect of α-lipoic acid on oxidative stress in adipose tissue of rats with obesity-induced insulin resistance, Cell. Physiol. Biochem. **2022,** 56, 239–253, doi.org/10.33594/000000528.

191. McNeilly, A. M., Davison, G. W., Murphy, M. H., Nadeem, N., Trinick, T., and McEneny, J. Effect of α-lipoic acid and exercise training on cardiovascular disease risk in obesity with impaired glucose tolerance, Lipids Health Dis. **2011,** 10, 1-9, doi.org/10.1186/1476-511X-10-217.

192. Arivazhagan, P., Ramanathan, K., and Panneerselvam, C. Effect of DL-α-lipoic acid on the status of lipid peroxidation and antioxidants in mitochondria of aged rats, J. Nutr. Biochem. **2001,** 12, 2–6, doi.org/10.1016/S0955-2863(00)00138-8.

193. Yawalkar, N. Drug hypersensitivity, Acta Clin. Belg. **2009,** 64, 529–533, doi.org/10.1179/acb.2009.090.

194. Gomaa, A. M. S., Abd El-Mottaleb, N. A., and Aamer, H. A. Antioxidant and anti-inflammatory activities of alpha lipoic acid protect against indomethacin-induced gastric ulcer in rats, Biomed. Pharmacother. **2018,** 101, 188–194, doi.org/10.1016/j.biopha.2018.02.070.

195. Brownlee, M. Biochemistry and molecular cell biology of diabetic complications, Nature **2001,** 414, 813-820, doi.org/10.1038/414813a.

196. Azevedo, Í. M., Lima, M. L., and Moreira, M. D. Effects of simvastatin on 5-fluorouracil-induced gastrointestinal mucositis in rats, Rev. Col. Bras. Cir. **2018,** 45, e1968, doi.org/10.1590/0100-6991e-20181968.

197. Kleniewska, P., and Pawliczak, R. The influence of apocynin, lipoic acid and probiotics on antioxidant enzyme levels in the pulmonary tissues of obese asthmatic mice, Life Sci. **2019,** 234, 116780, doi.org/10.1016/j.lfs.2019.116780.

198. Mims, J. W. Asthma: definitions and pathophysiology, Int. Forum Allergy Rhinol. **2015,** 5, 2-6, doi.org/10.1002/alr.21609.

199. Sook Cho, Y., Lee, J., Lee, T.H., Young Lee, E., Lee, K.U., and Moon, H.B. α-Lipoic acid inhibits airway inflammation and hyperresponsiveness in a mouse model of asthma, J. Allergy Clin. Immunol. **2004,** 114, 429–435, doi.org/10.1016/j.jaci.2004.04.004.

200. Dhar, D., Baglieri, J., Kisseleva, T., and Brenner, D. A. Mechanisms of liver fibrosis and its role in liver cancer, Exp. Biol. Med. **2020,** 245, 96-108, doi.org/10.1177/1535370219898141.

201. El-Senousey, H. K., Chen, B., Wang, J. Y., Atta, A. M., and Nie, Q. H. Effects of dietary vitamin C, vitamin E, and alpha-lipoic acid supplementation on the antioxidant defense system and immune-related gene expression in broilers exposed to oxidative stress by dexamethasone, Poultry Sci. **2018,** 97, 30–38, doi.org/10.3382/ps/pex298.

202. Morini, M., Roccatagliata, L., Dell'Eva, R., Pedemonte, E., Furlan, R., and Uccelli, A. α-Lipoic acid is effective in prevention and treatment of experimental autoimmune encephalomyelitis, J. Neuroimmunol. **2004,** 148, 146–153, doi.org/10.1016/j.jneuroim.2003.11.021.

203. Li, Y., Ma, Q.G., Zhao, L.H., Wei, H., Duan, G.X., and Ji, C. Effects of lipoic acid on immune function, the antioxidant defense system, and inflammation-related genes expression of broiler chickens fed aflatoxin contaminated diets, Int. J. Mol. Sci. **2014,** 15, 5649–5662, doi.org/10.3390/ijms15045649.

204. Prathima, P., Venkaiah, K., Reddy, M. H., and Sainath, S. B. Antioxidant effects of α-lipoic acid against epididymal oxidative damage in adult offspring rats exposed to maternal hypothyroidism stress, Reprod. Toxicol. **2024,** 125, 108555, doi.org/10.1016/j.reprotox.2024.108555.

205. Sastre, J., Pallardó, F. V., Plá, R., Pellín, A., Juan, G., and Viña, J. Aging of the liver: age-associated mitochondrial damage in intact hepatocytes, Hepatology **1996,** 24, 1199-1205, doi.org/10.1002/hep.510240536.

206. Jungwirth, A., Giwercman, A., Tournaye, H., Diemer, T., Kopa, Z., and Krausz, C. European association of urology guidelines on male infertility: the 2012 update, Eur. Urol. **2012,** 62, 324–332, doi.org/10.1016/j.eururo.2012.04.048.

207. Gharagozloo, P., and Aitken, R. J. The role of sperm oxidative stress in male infertility and the significance of oral antioxidant therapy, Hum. Reprod. **2011,** 26, 1628–1640, doi.org/10.1093/humrep/der132.

208. Ibrahim, S. F., Osman, K., Das, S., Othman, A. M., and Rahman, M. P. A. A Study of the antioxidant effect of alpha lipoic acids on sperm quality, Clinics **2008,** 63, 545–550, doi.org/10.1590/S1807-59322008000400022.

209. Di Tucci, C., Galati, G., Mattei, G., Bonanni, V., Capri, O., and Benedetti Panici, P. The role of alpha lipoic acid in female and male infertility: a systematic review, Gynecol. Endocrinol. **2021,** 37, 497–505, doi.org/10.1080/09513590.2020.1843619.

210. Asci, H., Erol, O., Ellidag, H. Y., Tola, E. N., and Ozmen, O. Pathology of cigarettes on the reproductive system and ameliorative effects of alpha lipoic acid: a rat model study, Toxicol. Ind. Health **2018,** 34, 385–395, doi.org/10.1177/0748233718755160.

211. Genazzani, A. D., Prati, A., Marchini, F., Petrillo, T., and Simoncini, T. 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. **2019,** 35, 1088–1093, doi.org/10.1080/09513590.2019.1640200.

212. Fruzzetti, F., Benelli, E., Fidecicchi, T., and Tonacchera, M. Clinical and metabolic effects of alpha-lipoic acid associated with two different doses of myo-inositol in women with polycystic ovary syndrome, Int. J. Endocrinol. **2020,** 1–8, doi.org/10.1155/2020/2901393.

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

214. Emir, D. F., Ozturan, I. U., and Yilmaz, S. Alpha lipoic acid intoxicatıon: an adult, Am. J. Emerg. Med. **2018,** 36, 1125-e3, doi.org/10.1016/j.ajem.2018.03.022.

215. Vidović, B., Milovanović, S., Stefanović, A., Takić, M., and Dordević, B. Effects of alpha-lipoic acid supplementation on plasma adiponectin levels and some metabolic risk factors in patients with schizophrenia, J. Med. Food **2017,** 20, 79-85, doi.org/10.1089/jmf.2016.0070.

216. Schuff-Werner, P., Pönisch, W., and Kaiser, T. Transient Howell-Jolly-body-like cytoplasmic inclusions in neutrophils after severe intoxication with alpha-lipoic acid, Scand. J. Clin. Lab. Invest. **2021,** 81, 8–11, doi.org/10.1080/00365513.2020.1855468.

217. Gatti, M., Ippoliti, I., Poluzzi, E., Antonazzo, I. C., Moro, P. A., and Raschi, Assessment of adverse reactions to α-lipoic acid containing dietary supplements through spontaneous reporting systems, Clin. Nutr. **2021**, 40, 1176–1185, doi.org/10.1016/j.clnu.2020.07.028.