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RESEARCH ARTICLE

Alpha-lipoic Acid: An Antioxidant with Anti-Aging Properties for Disease Therapy

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Abstract: The anti-aging effects of alpha-lipoic acid (αLA), a natural antioxidant synthesized in human tissues, have attracted a growing interest in recent years. αLA is a short-chain sulfur-containing fatty acid occurring in the mitochondria of all kinds of eukaryotic cells. Both the oxidized disulfide of αLA and its reduced form (dihydrolipoic acid, DHLA) exhibit prominent antioxidant function. The amount of αLA inside the human body gradually decreases with age resulting in various health disorders. Its lack can be compensated by supplying from external sources such as dietary supplements or medicinal dosage forms. The primary objectives of this study were the analysis of updated information on the latest two-decade research regarding the use of αLA from an anti-aging perspective. The information was collected from PubMed, Wiley Online Library, Scopus, ScienceDirect, SpringerLink, Google Scholar, and clinicaltrials.gov. Numerous *in silico, in vitro, in vivo*, and clinical studies revealed that αLA shows a protective role in biological systems by direct or indirect reactive oxygen/nitrogen species quenching. αLA demonstrated beneficial properties in the prevention and treatment of many age-related disorders such as neurodegeneration, metabolic disorders, different cancers, nephropathy, infertility, and skin senescence. Its preventive effects in case of Alzheimer's and Parkinson's diseases are of particular interest. Further mechanistic and clinical studies are highly recommended to evaluate the wide spectrum of αLA therapeutic potential that could optimize its dietary intake for prevention and alleviation disorders related to aging.

Keywords : Free radicals, chelating metals, detoxification, neurodegeneration, atherosclerosis, obesity, diabetes, cancer, skin senescence, nephropathy, infertility, dosage forms, nanoformulations.

1. INTRODUCTION

Aging is one of the most complex biological processes in multicellular organisms. It is associated with a decrease in physiological activities, a disruption in homeostasis of proteins and some other macromolecules, and increased chances of cell death [1]. As human beings age, the risk of neurodegenerative disorders, cardiovascular diseases, and cancer increases as a result of the altered countering mechanisms of the cell metabolic processes [2]. Thus, slowing down aging and reaching maximum lifespan are the most necessities for humans [3].

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One of the most common causative agents of aging is the excessive production of reactive oxygen species (ROS) that are formed during respiratory processes in mitochondria, as an attempt to maintain the organism's homeostasis [4, 5]. Even though aging is a natural phenomenon, it is often accelerated by the accumulation of ROS. There is no doubt that in case if the body's internal antioxidant system fails to provide antioxidant protection, then external antioxidants should be taken. Stabilizing some diseases and slowing down senescence may be reached by using appropriate dietary compounds and/or pharmacological substances [3]. The consumed antioxidants could be capable of sequestering free radicals, improving stress resistance, and eventually delaying the aging process.

Some dietary supplements have been proven to cause a delay in aging and a decrease in acquiring age-related diseases such as Alzheimer's disease, cancer, and cardiovascular disorders [6]. Such antioxidants as vitamins (A, C, and E), polyphenols (curcumin, resveratrol, quercetin, *etc.*) melatonin, astaxanthin, and alpha-lipoic acid (*α*LA) have been widely used to reduce ROS production in cells, and thereby reducing their harmful effects [1, 3, 7-10].

*α*LA is one of the highly effective antioxidants that are used to inhibit ROS production [11]. It is formed in the mitochondria of the cells and plays a crucial role in maintaining the homeostasis of the body [11]. αLA is an important cofactor in the overall process of cellular energy generation [12]. αLA is synthesized enzymatically in mitochondria and plays a cardinal role in their functioning [12]. However, some quantity of *α*LA could be also obtained from the diet and stored in many tissues [12]. At the cellular level, *α*LA acts as an antioxidant and anti-inflammatory agent, and its beneficial role in age-related neurological and muscular disorders have been well-documented.

Dietary intake of αLA appears to be clinically safe because it is a natural molecule [13]. αLA was added to the Italian list of authorized supplements by the Ministry of Health as a unique endogenous and exogenous antioxidant [14-16]. As it was found recently, such nutritional antioxidants as αLA and some polyphenols can reprogram metabolism, exerting anti-diabetic and anti-tumor effects [17].

Generally, αLA serves as a substrate for the enzyme pyruvate dehydrogenase and alfa-ketoglutarate dehydrogenase which plays essential roles in producing energy [18, 19]. It exhibits antioxidant properties by neutralizing free radicals, which are unstable molecules that can damage cells and contribute to aging and various age-related diseases. By scavenging free radicals, αLA helps in reducing oxidative damage to cells and tissues, potentially slowing down the aging process [20]. This property also makes it beneficial in skincare products due to its potential to protect against skin aging caused by oxidative stress. Studies suggest that *α*LA may also support the body's natural antioxidant defenses by recycling other antioxidants [21]. Therefore, *α*LA was named as 'an antioxidant of antioxidants' namely such as oxidized forms of vitamins C and E, glutathione and coenzyme Q10 [14, 15].

αLA enters biological membranes easily due to its affinity with membrane lipids, as well as the blood--brain barrier, which confers to *α*LA a potential neurodegeneration-preventive activity [21-23]. Unlike many other antioxidants, its oxidized form that formed upon reaction with various pro-oxidants and free radicals can easily reconstitute to dihydrolipoic acid (DHLA) [14]. Furthermore, αLA and DHLA are amphipathic molecules and can, therefore, work both in aqueous and hydrophobic environments, explaining that they can counteract the oxidation of lipids, proteins, and DNA [24]. The complexes of αLA/DHLA are powerful in recycling endogenous antioxidants. They significantly improve mitochondrial function and regulate the expression of genes involved in aging.

Different beneficial roles of αLA were explored in various therapeutic regimens [25-27]. In recent years, αLA has been studied extensively as a powerful antioxidant and detoxification agent [11]. It has also been claimed to ameliorate age-associated cognitive, cardiovascular, and neuromuscular deficits besides being implicated as a modulator of various inflammatory signaling pathways [12, 25-27].

Several clinically useful characteristics of αLA have anti-obesity and hypolipidemic effects and participate in enhancing glucose metabolism [28, 29]. Additionally, because of its high antiproliferative and cytotoxic properties, it is effective against multiple types of cancer, has a regenerative effect, speeds up wound healing, and is helpful in cases of nephropathy as well as female and male infertility [30, 31]. Besides being an important enzymatic cofactor, it manages gene transcription and chelates heavy metals [11]. For instance, αLA can successfully prevent Hg toxicity [32]. Recently, Barletta *et al.* [33] found the efficacy of the use of coenzyme Q10 combined with αLA in reducing chronic COVID-19 syndrome. Thus, αLA is a compound that acts primarily as a powerful antioxidant in the body, aiding in the protection against oxidative stress, which can contribute to various diseases and the aging process.

This study aimed to analyze the modern data regarding the use of αLA as a powerful antioxidant from an

anti-aging perspective. Numerous *in vitro, in vivo,* and clinical studies, mainly from the 20-year latest scientific publications, were proceeded from Pubmed, Scopus, Wiley Online Library, ScienceDirect, SpringerLink and clinicaltrials.gov. Several keyword combinations, including alpha-lipoic acid and aging, senescence, neurodegeneration, cancer, *etc.*, were used. To ensure the inclusion of relevant publications, specific selection criteria were applied during the initial screening.

2. αLA: ORIGIN, BIOCHEMISTRY AND MAIN PROPERTIES

αLA is a natural organo-sulfur (dithiol) compound, also known as thioctic acid or 1,2-dithiolane-3-pentanoic acid [11]. αLA was originally isolated from bovine liver in 1951 [14, 15]. It is synthesized from octanoic acid and cysteine in the mitochondria of eukaryotic cells [16]. αLA is usually produced endogenously in the body and is essential for aerobic metabolism [34].

αLA contains two sulfur atoms at C6 and C8 connected with a disulfide bond that makes it oxidized. It has one chiral center (C6), which makes it exist in two (R and S) enantiomeric forms [34]. The *α*LA of natural origin exists as the R-enantiomer while the synthetic one consists of a racemic mixture of both R and S forms [11]. Of the two enantiomers, only R-enantiomer can covalently conjugate to conserved lysine residues through an amide linkage, thus being considered as the real essential cofactor for biological systems [35]. The reduced form of *α*LA is called DHLA which contains a pair of thiol groups (Fig. **1**). The experimental kinetic research demonstrated that *α*LA is capable of scavenging very reactive radicals, while the HDLA can scavenge *via* a hydrogen transfer mechanism because in water it is deprotonated, which enhances its activity [36].

As it was reported, *α*LA can be found in almost all foodstuffs, although its amount is very low. A higher amount of αLA is usually found in kidneys, liver, meat, eggs, broccoli, spinach, canned peas and yeast extract [37]. Thus, although in a very low quantity, the common dietary sources of αLA are some foods of animal origin as well as fruits and vegetables [37, 38]. However, the supplementation of αLA is almost completely derived from the chemically synthesized sources.

Previous studies reported multimodal transporters to be responsible for *α*LA uptake. In CaCo2 cells, the *α*LA could traverse rapidly into the cell monolayer, depending on pH [39]. Due to the various mechanisms involved in *α*LA transport, the bioavailability of *α*LA varies depending on the state of the compound, as well as whether it is taken with a meal or as a dietary supplement.

In light of its pharmacokinetic characteristics, αLA has a relatively modest therapeutic efficacy, a brief half-life and bioavailability of about 30% [40], because of its degradation in the liver, decreased solubility, and instability in the stomach. However, the bioavailability of αLA greatly increased by the application of several novel formulations [41]. The synthesis of new *α*LA composites increased photo- and thermal stability, pharmacological effectiveness and safety [42].

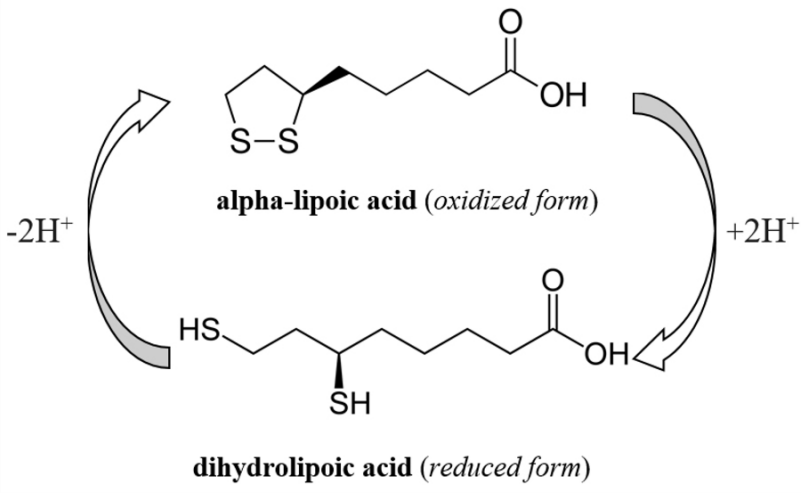

Fig. (1). Chemical structures of *α*LA and DHLA. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Due to the hydrophilic and lipophilic characteristics of the αLA molecule, it is considered the most effective antioxidant that rapidly spreads in cell membranes and cytoplasm of cells and has a pharmacological effect by activating anti-inflammatory pathways [11]. αLA contributes to the reduction of abnormal oxidative stress and has a protective effect in type 2 diabetes mellitus (T2DM) and vascular atherosclerosis [43]. The chelating properties, regeneration capacity, coenzyme activity, and signal transmission through various routes should be also considered to support the pleiotropic effects of αLA in different pathways related with several diseases [44-47].

3. αLA AND DHLA IN REDUCING ROS LEVEL AND INFLAMMATION

As it is known, ROS are formed during respiratory processes and their excessive quantity is one of the most common causes of aging. The excessive ROS production can result in the oxidation of proteins, DNA, RNA, and plasma membrane [4, 48]. ROS is involved in many pathological conditions including T2DM, cancer, neurodegeneration, cardiovascular disorders, skin aging, etc [2].

*α*LA and its reduced form, DHLA, can scavenge ROS, directly and indirectly, to protect cells against oxidative stress and also improve the cell resistance to conditions where oxidative stress is involved, thereby preventing aging [12, 14, 15, 21, 49]. By detoxifying ROS, these antioxidants play a decisive role in maintaining homeostasis and management of a lot of age-related disorders (Fig. **2**).

Due to its antioxidant capabilities, αLA lowers ROS levels and prevents ROS-mediated DNA damage *in vitro* and *in vivo,* also reduces 8-hydroxy-2'-deoxyguanosine levels a biomarker of oxidative damage, increases the body's immune system defenses [50, 51]. Restoring the intracellular redox state inhibits inflammation and subsequently tumor progression. Therefore, antioxidants like αLA could be considered as potential anticancer substances [52, 53].

*α*LA also helps to restore the levels of the glutathione system inside the cell hence boosts the free-radical scavenging capabilities of the cell [12]. It has been shown that *α*LA administration prevents aging in heart muscles and can be useful in managing age-related deterioration in heart functions [54]. In another study, αLA administration has been shown to improve the antioxidant status of the cell by increasing the levels of another potent antioxidant ascorbic acid. This enhanced anti-oxidative capacity prevented DNA damage in heart cells and ameliorated age-related oxidative stress [55].

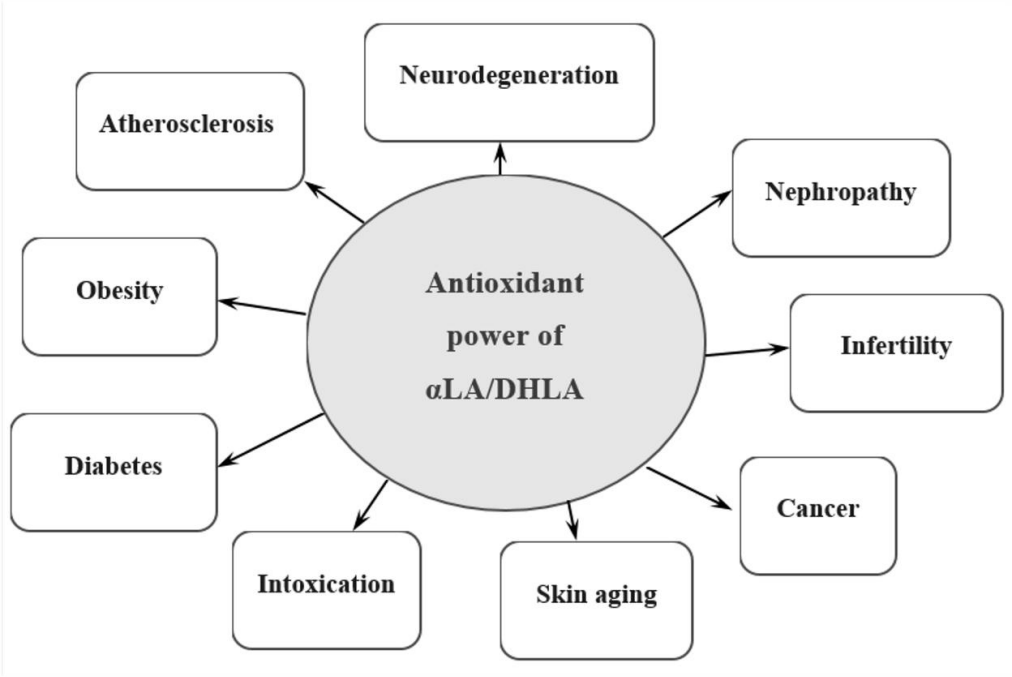

Fig. (2). Antioxidant potential of αLA/DHLA in coping with age-related disorders. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

It has been demonstrated that αLA and DHLA can reduce inflammatory activity, levels of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), IL-1, IL-6, IL-17, and IL-18, interferon as well as the oxidation of several antioxidants [56-58]. *α*LA suppresses the inflammatory response by inhibiting molecular signaling pathways activated by proinflammatory cytokines, such as TNF-α, which is a key activator of the NF-kB pathway [15]. NF-kB can be activated by a diverse range of stimuli in most cell types, including ROS [59]. This pathway mediates inflammatory responses and regulates the expression of several inflammatory mediators, including chemokines, cytokines and cytokine receptors [15]. In addition, NF-kB modulates different inflammatory cytokines, including IL-1b and IL-6 [60]. Moreover, NF-kB is considered to play a pivotal role in the progression of atherosclerosis. It was found that *α*LA inhibited NF-kB activation and adhesion molecule expression in human aortic endothelial cells [59].

The experimental studies on the model of peptic ulcer disease showed that the therapeutic effect of indomethacin on mucosal malondialdehyde (MDA) was significantly better in combination with *α*LA (100 mg/kg) [61]. These studies were regarded as a base for clinical trials of gastric ulcer protection of *α*LA when there is a simultaneous oral administration of anti-inflammatory medicinal products. LA induced the DNA methylation in the 5'-flanking regions of the IL-1β and IL-6 genes in the cultivated SK-N-BE human neuroblastoma cells and decreased mRNA expression and as a consequence, a decrease in the cytokine release in the culture medium. These data could be a starting point for the possible usage of *α*LA in the preventive management of aging [60].

It could be concluded that the lipid-lowering effects of αLA are often associated with its antioxidant and anti-inflammatory properties. By reducing oxidative stress and inflammation, αLA has a positive effect on lipid metabolism and prevents lipid peroxidation, which contributes to the development of atherosclerosis [62], because the pathogenesis of vascular atherosclerosis is based on immunoinflammatory reactions [63].

4. THE ROLE OF αLA IN COPING DIFFERENT DISORDERS RELATED TO AGING

4.1. Neurodegeneration

All over the world, scientists note the growth of neurodegenerative diseases among the population [64]. Disorders such as Alzheimer's disease, Parkinson's disease, stroke, and spinal cord injury occur most often in people over 50 years of age and lead to severe physical and mental disability. These diseases are associated with the degeneration or death of certain groups of nerve cells and, as a result, gradually increasing atrophy of the corresponding parts of the brain, which leads to dementia and impaired movement in humans. As a result of endoplasmic reticulum stress and mitochondrial dysfunction, the brain suffers and, as a result, accelerated aging of the body occurs [65]. αLA has a neuroprotective effect by preventing the excessive formation of ROS and improving the functions of mitochondria, therefore, it is used as an additive in neurodegenerative diseases [66]. The use of αLA in patients with Alzheimer's disease improves the condition of patients and slows down cognitive impairment [64]. Similar approaches have been outlined for the prevention and treatment of Parkinson's disease and multiple sclerosis, but the mechanisms of action of αLA have not yet been fully established [67].

Recent studies revealed that αLA has great potential to relieve age-related neurodegenerative disease and cognitive impairment [68]. The aging mice which received αLA for two months demonstrated enhancement in their cognitive function. The proteomic analysis using liquid chromatography-mass spectrometry/-mass spectrometry tools established that the levels of 10 proteins were improved significantly [68]. αLA prevented the loss of memory in the experimental rats through the neuromodulatory mechanisms [69]. This molecule manifests its neuroprotective effect by inhibiting ROS formation and following neuronal damage as well as promoting neurotransmitters [70]. Moreover, αLA could readily cross the blood-brain barrier, which is an important factor for its brain activities [70].

Alzheimer's disease occurs as a result of oxidative stress damage to critical neuronal cells, and it is directly related to aging. The ROS causes damage to the plasma membrane, mitochondria, and nucleic acids by overwhelming the endogenous antioxidants, hence, preceding the neuropathologic alterations [71, 72]. Since the pathologic process of Alzheimer's disease begins with the oxidative damage of neuronal cells, antioxidants such as αLA and vitamin E have been proven to be viable therapeutic targets that result in the delay of onset of the disease [71, 73] and, hence, delaying aging ultimately.

It is no doubt that the prevalence of Alzheimer's disease in the aging population imposes a heavy burden on the patients' families and society. It was found that αLA can attenuate cell toxicity provoked by amyloid beta fragment ($A\beta_{25-35}$)-induced PC12. Such an $A\beta_{25-35}$

treatment largely decreased the viability of PC12 cells and rescued $A\beta_{25-35}$-induced neurotoxicity through the Wnt-β-catenin pathway [74].

As it is known, symptomatic therapy of Parkinson's disease is based on the correction of neurochemical imbalance in the basal ganglia, which is characterized by a decrease in dopamine levels due to the degeneration of nigrostriatal neurons and an increase in the activity of cholinergic and glutamatergic systems. In patients with neurodegenerative diseases, the content of iron in the brain is high. Tissues with high oxygen consumption require iron, which is a metabolic cofactor. In excess amounts, iron generates ROS, and participates in the redox reaction. As a result, there is a violation of iron homeostasis in neurons, which leads to their death. αLA has high potential as a neuroprotective therapy. In the experiment, it was proved that αLA attenuates the accumulation of iron and reduces the level of intracellular ROS, which may be associated with the regulation of iron homeostasis and a decrease in the level of oxidative stress. αLA also promotes the survival of dopaminergic neurons [75].

The mechanism of αLA in regulating ferroptosis was recently evaluated in the Parkinson's disease experimental model [76]. It was found that αLA can ameliorate motor deficits in Parkinson's disease models and regulate iron metabolism by upregulating ferritin heavy chain 1 and ferroportin as well as down-regulating iron importer metal transporter 1.

According to animal studies, αLA can reverse scopolamine-induced memory impairment and neurodegeneration by restoring neuronal cell loss, which is mediated by its antioxidant positive modulation of astrocyte-neuron interaction during neuroinflammation in response to oxidative tissue damage [77]. Another *in vivo* investigation discovered that αLA could successfully reduce the apoptosis and morphological changes of BV2 microglial cells stimulated by amyloid-β, in addition to the inhibition of the inflammatory reaction, suggesting that αLA may have protective effects on nerve cells [74]. It has been found *in vitro* and *in vivo* models of iron overload that *α*LA can reduce toxicity in the microglial cell line HMC3 by preventing apoptosis cells, the formation of ROS, and reducing the depletion of glutathione [78]. In addition to *in vivo* and *in vitro* models of Parkinson's disease [79, 80], the neuroprotective effect of αLA acid was proven in Alzheimer's disease patients whose cognitive skills were assessed on multiple scales [81, 82].

Other scientists [83] have also conducted studies evaluating the effects of αLA on various cognitive functions in healthy older adults. The randomized, double-blind, placebo-controlled clinical trial involved 60 patients, who were randomized to receive flaxseed oil containing 2.2 g of αLA. After 12 weeks of use, a significant improvement in cognitive function was noted. Further validation studies examining the effects of αLA on verbal fluency and executive function in older adults are needed because verbal fluency is a predictor of Alzheimer's disease that is important for cognitive health.

Unfortunately, memory disorders are very common among elder people, and cognitive decline occurs in connection with the onset of aging. Basile *et al.* [84] observed 15 elderly patients (over 75 years old without a diagnosis of cognitive impairment) who received αLA at a daily dose of 600 mg/day for 3 months. There were moderate positive effects of αLA found on cognition and mood. It demonstrated that treatment with αLA was able to improve the functioning of serotonin, dopamine and norepinephrine neurotransmitters [85]. It enhanced memory capacity in several experimental models of age-related cognitive decline in rodents.

Cognitive impairment is one of the complications associated with chemotherapy. Doxorubicin is a ROS-producing anticancer drug causing potential neurotoxic effects [86]. It was concluded that αLA (200 mg/kg administered for 4 weeks) offers neuroprotection against doxorubicin-induced cognitive impairment, which could be attributed to its high antioxidant potential. The neuroprotective effect of αLA (200 mg/kg body weight) on radiation-induced brain-stem injury in rats was experimentally revealed by Motallebzadeh *et al.* [87]. The *in vitro* study investigated the enhancing effect of αLA on phagocytosis of beta-amyloid $(oA\beta)_{1-42}$ in BV-2 microglial cells [88].

An *in vivo* experiment was conducted on rats [89] to evaluate the role of αLA in reducing the manifestations of brain resistance to insulin. The authors found that αLA improved the function of the brain's enzymatic and non-enzymatic antioxidant systems, but the protective effects of αLA were observed primarily in the hypothalamus of insulin-resistant rats. The protective effects of αLA are due to the activation of the hypothalamic transcription factor Nrf2 and the inhibition of NF-κB.

The effect of seizures on performance and acetylcholinesterase/choline acetyltransferase activities in Wistar rats' hippocampus was investigated by de Freitas [90]. Rodents were treated with αLA (20 mg/kg, intraperitoneally), pilocarpine (400 mg/kg, intraperitoneally), and the association of αLA (20 mg/kg) plus

pilocarpine (400 mg/kg). It was concluded that αLA can reverse cognitive dysfunction observed in rats and increase the acetylcholinesterase/choline acetyltransferase activities in the hippocampus before pilocarpine-induced seizures, suggesting that it could be used in the treatment of epilepsy [90].

As it was recently concluded, the analgesic potential of αLA in coping with chronic neuropathic pain is due to its multiple antioxidant mechanisms [91]. Rodrigues *et al.* [92] found that αLA treatment (100 mg/kg orally for 15 days) prevents nociception due to its ability to reduce oxidative stress and neuroinflammation in a model of complex regional pain syndrome type I in mice. Repeated αLA treatment reduced the chronic post-ischemia pain injury in mice provoked by cold and mechanical allodynia and restored nest-building behavior without causing locomotor alteration [92].

Thus, αLA as a neuroprotective antioxidant can prevent excessive formation of free radicals and improve the functioning of key cell organelles. Therefore, it could be effectively used in the prevention of neurodegenerative diseases. It has great potential to prevent age-related neurodegenerative disorders and cognitive impairments.

4.2. Atherosclerosis

αLA may help improve markers of metabolic syndrome, a group of conditions including high blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels [93, 94]. Although αLA did not specifically target atherosclerosis, it assessed markers such as C-reactive protein and TNF-α levels that are indirectly associated with cardiovascular risk factors.

Endothelial dysfunction is recognized as an early sign of systemic atherosclerosis and represents a therapeutic target to prevent long-term cardiovascular consequences. As a result of dysfunction, endothelial cells lose their regulatory ability and the production of various biologically active substances is not regulated, which leads to inflammatory processes and thrombus formation in the vessels. Oxidative stress damages mitochondria, cellular DNA, endoplasmic reticulum, and cell membranes, increases the expression of endothelial adhesion molecules, resulting in chronic inflammatory processes [63]. As a result, atherosclerotic plaques form on the walls of blood vessels.

Studies show that in obese people suffering from heart and metabolic diseases, the accumulation of oxidized low-density lipoprotein (LDL) levels in the liver and the formation of foam cells from macrophages is due to the progression of [REMOVED HYPERLINK FIELD] non-alcoholic fatty liver disease (NAFLD) and excessive formation of ROS and reactive nitrogen species (RNS) [95, 96].

Tromba *et al.* [43] conducted experimental studies on the effect of αLA on endothelial function and cardiovascular risk factors in overweight/obese young adults. The experiment was a double-blind, placebo--controlled, randomized trial of 67 overweight children who were randomly assigned to receive αLA for three months. The results showed that αLA supplementation improved vascular tone, and significantly reduced insulin resistance and LDL levels in obese children [43].

The findings of antioxidant/atherosclerosis mouse model suggested a potentially preventive and therapeutic approach for the clinical application of αLA for atherosclerosis treatment *via* immune regulation of suppression inflammatory response, including an increase in the population of Treg cells and levels of circulating auto antibodies, as well as a decrease in T cell infiltration [97]. In a double-blind, placebo-controlled clinical trial, 70 diabetic patients were randomly assigned to αLA (1200 mg αLA as two 600 mg capsules/day) or placebo. Results showed a positive correlation between a decrease in oxidized LDL and a particular vascular inflammation biomarker, which is carried by lipoproteins in the blood and plays a significant role in the pathogenesis of atherosclerosis [98].

It was indicated [99] that αLA may help in lowering lipid levels and potentially prevent or mitigate atherosclerosis. Research into the lipid-lowering effects of αLA over the past 5 years has led to several notable discoveries and advances [100, 101]. Some of randomized controlled trials have shown that αLA supplementation reduces blood glucose concentrations and/or improves insulin sensitivity [102, 103]. Although studies in animal models also report fairly consistent reductions in both blood and tissue lipid levels in response to αLA supplementation [104-106], human studies have not yet provided conclusive results and require further investigation.

The *in vitro* experiments [107] showed that αLA may regulate enzymes involved in lipid metabolism, such as acetyl-CoA carboxylase and fatty acid synthase. αLA appeared to inhibit these enzymes, potentially impacting lipid synthesis and accumulation. *in vitro* studies on 3T3-L1 adipocytes indicated that αLA treatment reduced inflammation markers and improved insulin sensitivity in adipocytes [108, 109]. *in vitro* experiments using HepG2 cells suggested that αLA treatment increased the expression of Sirt1, associated with

improved lipid metabolism and reduced lipid accumulation [110]. In another experience, authors [111] created a liver fat cell model by incubating HepG2 cells in high glucose (30 mM glucose) and high fat (0.1 mM palmitate) media. As a result, it was found that the activation of the monophosphate-activated protein kinase signaling pathway induces ATGL protein expression and enhances lipid hydrolysis. Similarly, the treatment of a liver fat cell model with αLA decreased intracellular lipid accumulation in HepG2 cells, increased monophosphate-activated protein kinase phosphorylation, and induced ATGL expression. αLA has been shown to dephosphorylate FOXO1 and reverse nuclear exclusion of FOXO1. These data suggest that αLA can effectively improve intracellular lipid accumulation and induce ATGL expression through the FOXO1/ATGL pathway in liver cells. Thus, αLA may be a potential therapeutic agent for the treatment of fatty liver disease. This could play a role in regulating lipid levels, which may contribute to reducing the risk of atherosclerosis [102]. However, it is important to note that while these findings are promising and offer insights into αLA's potential mechanisms, *in vitro* studies have limitations. The results may not always translate directly to human responses, and further research, especially in clinical settings, is necessary to validate these effects and understand their clinical significance in treating diseases or conditions.

Various mechanisms by which αLA exerts its lipid-lowering effects have been studied [62]. These mechanisms include the regulation of enzymes involved in lipid metabolism, modulation of gene expression associated with lipid homeostasis, increased insulin sensitivity, and improved mitochondrial function, all of which contribute to its lipid-lowering properties. Studies on rabbits have shown that αLA (100 mg/day) exhibits lipid-lowering and antiatherosclerotic properties, as evidenced by low levels of plasma total cholesterol and LDL and a reduction in the formation of atherosclerosis-induced lesions in experimental animals.

In atherosclerotic mice [112], αLA treatment was found to inhibit atherosclerosis progression by enhancing cholesterol efflux mechanisms *via* upregulation of ATP-binding cassette transporter A1/G1, crucial proteins involved in cholesterol transport. αLA suppressed oxidized LDL-induced lipid accumulation was reversed by geranylgeranyl pyrophosphate or liver X receptor α siRNA treatment. In conclusion, liver X receptor α-dependent activation of ATP-binding cassette transporter A1 and ABCG1 may mediate the beneficial effects of αLA on foam cell formation.

In an animal model of cardiac hypertrophy, αLA treatment showed protective effects by reducing oxidative stress and inflammation markers, which are relevant factors in atherosclerosis development and progression. Experimental evidence suggests that αLA plays a beneficial role in protecting the heart from adverse effects of chronic pressure overload. A mouse model study [113] was used to examine the role of αLA-DHLA in heart failure injury and mitochondrial damage. The following study showed that αLA may improve atherosclerosis by increasing HDL cholesterol levels through miR-124-mediated effects on ROCK1, an enzyme involved in the development of atherosclerosis [114].

It has been shown in clinical trials that αLA supplementation can have a positive effect on lipid profiles [115]. The experiment involved 46 patients with metabolic syndrome, who were randomly divided into two groups. One group of patients received 600 mg αLA, the other group received 600 mg placebo for 12 weeks. It was demonstrated to have the ability to lower total cholesterol, LDL cholesterol (considered the "bad" cholesterol), and triglyceride levels while increasing HDL cholesterol (considered the "good" cholesterol) in some people. These effects are critical for reducing the risk of atherosclerosis and cardiovascular diseases.

Manning *et al.* [116] conducted a one-year clinical trial of the effects of treatment with the antioxidant αLA with or without the addition of vitamin E on markers of insulin resistance and systemic inflammation, as well as plasma concentrations of non-esterified fatty acids in individuals with metabolic syndrome. One group of patients received αLA (600 mg/day), another group received vitamin E only (100 IU/da), and a third group received both αLA and vitamin E. As a result, these findings suggested that long-term use of αLA in combination with vitamin E may modestly reduce plasma nonesterified fatty acid concentrations but do not alter insulin or glucose levels in individuals with metabolic syndrome.

As it is commonly known, *in silico* experiments, including computer modeling and simulation, can provide insight into molecular interactions, pathways, and predictions of a compound's potential effects. However, data are limited for specific *in silico* studies of αLA associated with lipid-lowering effects and atherosclerosis. There are few in *silico* studies of αLA [117], which presented the results of molecular docking simulations for the development of a new series of niacin and αLA dimers. The selected combination of αLA and antihyperlipidemic drug results in better lipid modulation, higher synergistic effects and fewer side effects.

Generally, αLA shifts the spectrum of blood lipids towards unsaturated fatty acids, lowers cholesterol and saturated fatty acids in the blood, preventing the development of atherosclerosis.

4.3. Obesity

In today's world, obesity is rapidly accelerating among all segments of the population. Obesity is a multifactorial disease based on an imbalance between consumed and expended calories and a sedentary lifestyle. Violation of the energy balance is associated with the consumption of high-calorie foods with a high content of fats and sugars. A raised body mass index is a risk factor for serious diseases of the cardiovascular system (hypertension and coronary heart disease), the endocrine system (disturbances in the reproductive function of the body, T2DM), the musculoskeletal system, and the development of oncology. This leads to physical limitations, psycho-emotional disorders and even disability [118].

αLA may help in weight management by influencing certain metabolic pathways related to fat metabolism and energy production. Modern studies show that in the last decades, there has been an increase in obesity, which is associated with an increased severity of NAFLD. Today, NAFLD occurs in 90% of patients with morbid obesity and among 25-30% of the world's population [119]. NAFLD is a common chronic liver disease characterized by abnormal accumulation of fat droplets. The main feature of NAFLD is the absence of symptoms of the disease. As a rule, this disease is detected incidentally during laboratory or instrumental studies of analyses in patients with metabolic syndrome. Scientists believe that as obesity, T2DM and metabolic syndrome continue to skyrocket in the population, the morbidity and mortality associated with NAFLD will also rise [120].

Studies on the use of αLA in the treatment of NAFLD have shown that it leads to the activation of antioxidant defense mechanisms, thereby reducing inflammation in damaged tissues and preventing the development of fatty liver. αLA promotes the mobilization of fat from the fat depot of the body and its utilization in the process of energy metabolism. αLA prevents the formation of glycation end products and, as a result, the formation of active oxygen metabolites decreases, and oxidative stress in cells decreases [120]. NAFLD is common in diabetic and obese patients. It has been proven that αLA activates adenosine monophosphate protein kinase and thereby helps to reduce lipid accumulation in skeletal muscle. It improves glucose utilization by tissues, which is associated with the phosphorylation of tyrosine residues of insulin receptors and the activation of glucose transporters.

in vitro experiments using 3T3-L1 preadipocytes suggested that αLA treatment inhibited adipocyte differentiation by regulating pro-adipogenic transcription factors through MAPK pathways, potentially influencing obesity-related fat cell formation [121]. While not exclusively focused on obesity, this study examined αLA's protective effects on enzymes involved in lipid metabolism against oxidative and nitrosative stress. Such protection may have implications in preventing dysregulation of lipid metabolism associated with obesity [89, 122].

The study by Zhao and Hu [123] focused on evaluating the efficacy and safety of αLA in the treatment of geriatric T2DM complicated by acute cerebral infarction. However, this study in aged rats with T2DM revealed the potential of αLA to improve insulin sensitivity and metabolic functions, factors associated with obesity and metabolic disorders. These *in vitro* and *in vivo* studies collectively indicate that αLA's effects are multifaceted and may involve various mechanisms. These mechanisms include modulating gene expression, impacting cellular metabolism, reducing oxidative stress, and protecting cells against dysfunction.

The clinical studies [124] evaluated the use of αLA during exercise in obese patients with impaired glucose tolerance. The experiment involved 24 obese patients (BMI ≥ 30 kg/m2) with αLA. Participants were divided into two groups, the first received 5 days a week, while taking 1 g per day of αLA for 12 weeks with regular exercise. The second group received the same dose of αLA but without exercise. There was a high rate of LDL oxidation in the αLA-only group. However, the combination of exercise and αLA reduced LDL oxidation.

The αLA' supplementation may be beneficial to some degree in obesity and diabetes, modestly improve glycemic control and lipid profiles, as well as weight loss, without side effects, and are also beneficial for diseases such as cancer. There is little data on the lipid-lowering activity of αLA in foods (red meat, spinach, broccoli, tomatoes, peas, Brussels sprouts) because it is poorly bioavailable from plants, but research is ongoing.

A retrospective cohort study [125] combining αLA and *Crocus sativus* extract for the treatment of patients with carpal tunnel syndrome has been published. This combination showed a very pronounced neuroprotective effect on peripheral nerves and relief of neuropathic pain. The study included 201 patients who received

the drugs. The authors concluded that αLA combined with saffron appears to be effective in relieving pain associated with wrist disease. An example of a combination of αLA and linseed oil [126] to treat rats suffering from hyperlipidemia due to a high-fat diet found that this compound was able to mitigate side effects and inhibit hyperlipidemia in rats by improving plasma lipid levels [127].

As it was generally concluded, being overweight or obese is a serious risk factor for some types of cancers, including colon, pancreatic, breast and thyroid because more fat tissues can produce more hormones provoking tumors [128]. αLA was regarded as a useful agent in the chemoprevention of obesity-related cancers.

The analyzed studies offer insights into potential mechanisms by which αLA might impact obesity-related pathways. However, while promising, these findings warrant further investigation and validation through additional preclinical and clinical studies to establish the potential therapeutic use of αLA in managing obesity. These advances and discoveries highlight the potential of αLA as a supplement to improve lipid profiles and its possible role in reducing the risk of cardiovascular diseases.

4.4. Diabetes

The issue of early detection and treatment of diabetes mellitus, which is a metabolic disorder characterized by high blood glucose, is an urgent issue for modern medicine [129]. It is one of the most common non-infectious human diseases after cardiovascular and oncological pathology, leading to disability. T2DM is the most common disorder of the endocrine system, it is a chronic metabolic disorder that results in the lack of proper control of blood glucose due to absolute deficiency of insulin secretion, lack of insulin action, or both. It often results in the following major complications; microvascular and/or macrovascular complications [130]. The rapid growth of diabetes is associated with many influences including genetic and environmental factors. Physicians note the fact that about 50% of disease cases are not diagnosed in the early stages before complications occur. Patients with T2DM suffer from obesity and impaired lipoprotein metabolism, so they develop concomitant microvascular complications. This leads to deterioration of vision and blindness, poor wound healing, erectile dysfunction, atherosclerosis of blood vessels, kidney failure, heart disease, etc [129].

αLA plays an important role in the formation of energy (adenosine triphosphate), thus reducing the energy deficit in tissues and preventing the formation of advanced glycation end products, which reduces the severity of oxidative stress [131]. The ability of αLA to improve glucose utilization by tissues is associated with phosphorylation of tyrosine residues of insulin receptors, activation of glucose transporters GLUT-1 and GLUT-4, and several other effects in insulin-dependent tissues [132].

Sena *et al.* [133] conducted studies on the effect of αLA on endothelial function in Goto-Kakizaki diabetic and high-fat animal models. Rats had elevated plasma levels of glucose, insulin, and free fatty acids compared to their control counterparts. The results suggest that αLA restored endothelial function and improved systemic and local oxidative stress in high-fat fed Goto-Kakizaki diabetic rats. Specifically, αLA reduced total and non-HDL serum cholesterol and triglycerides, reversed MDA, carbonyl groups, and also reduced fasting circulating glucose concentrations and urinary albumin excretion. These beneficial effects were at least partially attributed to the recoupling of eNOS and increased NO bioavailability. The addition of αLA completely restored NO release and partially restored eNOS expression in aortic tissue. The study concluded that αLA has potential as a therapeutic agent for diabetic complications associated with T2DM and endothelial dysfunction.

Some studies have shown the direct correlation between diabetes and how it causes the imbalance between ROS and antioxidants produced by the body, resulting in oxidative damage of cellular components [134]. αLA can reduce the destruction rate of beta cells, increase sensitivity to insulin, and slow down complications (neuropathy) of diabetes mellitus [135-138]. In the hearts of T2DM rats suffering from ischemia/reperfusion injury, αLA intensifies the antiarrhythmic and cardioprotective effects of ischemic postconditioning [139].

Diabetic neuropathy is a frequent complication of diabetes, and varied mechanisms such as inflammation, metabolic disorders, and alternation in neuro-immune interactions could lead to its development [140]. The histological examination showed less myelin loss in the sciatic nerves of experimental animals in the group treated with αLA. The oral-administered αLA (dosages 600-1800 mg/day) could ameliorate the symptoms of sensorimotor peripheral neuropathy in diabetic patients by reducing oxidative stress and improving microcirculation in a dose-dependent manner [141]. In another study, the authors [142] evaluated the use of αLA to prevent the development of diabetic neuropathy. The study included patients with T2DM, with moderate to severe diabetic polyneuropathy of the lower ex-

tremities, as well as a control group without microvascular complications. The neuropathy group received αLA infusion therapy. The authors claim that they were able to achieve a decrease in the levels of oxidative markers, and also established a connection between markers of oxidative damage to lipids and proteins and some parameters of vascular stiffness.

Generally, numerous *in vitro*, *in vivo* and clinical studies revealed good antidiabetic potential of αLA. However, further research, including large-scale clinical trials, is needed to fully understand its effectiveness, optimal dosage and long-term effects.

4.5. Intoxication

Many diseases are associated with an excessive accumulation of different toxic compounds in the body during life [143]. Thus, scientists, physicians, and patients are especially interested in finding natural compounds that increase a healthy lifespan by detoxifying the body.

αLA has a variety of protective properties, including improved enzymatic and non-enzymatic antioxidant systems, a decrease in inflammation and apoptosis as well as can stimulate the production of glutathione, which may be able to prevent liver oxidative damage [58, 89, 144]. Among other sulfur-containing compounds (sulforaphane, S-allyl cysteine and ergothioneine), ALA demonstrated effectiveness in preventing liver fibrosis [145, 146]. The current *in vivo* study showed that αLA can protect against liver damage caused by cyclosporine A, restoring antioxidant levels in serum and liver tissues, reducing the recruitment of inflammatory markers, and inhibiting apoptosis [147].

In liver cirrhosis, oxidative stress increases and as a result, glutathione levels decrease and a lipid peroxidation marker increases [148]. αLA restores glutathione reserves, promotes the release of cytochrome and prevents cell death. Thus, the appointment of αLA is pathogenetically justified in the treatment of toxic liver diseases [149].

αLA increases the activity of the enzyme mitochondrial aldehyde dehydrogenase-2, which is responsible for the oxidation of acetaldehyde during the metabolism of ethanol, as well as for the oxidation and neutralization of aromatic and aliphatic aldehydes [150, 151]. In recent decades, toxic liver damage has become increasingly common among the population, which may be associated with the intake of poor-quality food, alcohol, drugs, endocrine, chronic and viral diseases, as well as exposure to environmental toxicants, including pesticides, fungicides, and heavy metals.

Given the fact that αLA easily penetrates the cell and can chelate heavy metals, and form complexes that are easily excreted without redistribution to other organs or tissues, studies have been conducted on the use of αLA in case of metal intoxication and poisoning by toxic fungi [152]. αLA chelates toxic metals such as cadmium, lead, nickel, arsenic, mercury, and copper. DHLA, as a reduced form of αLA, has a direct binding effect on heavy metals. Based on experimental data, DHLA has been proposed as an antidote for mercury poisoning [32, 152, 153].

Recently, Bai *et al.* [154] found that oral gavage with αLA (for 7 days, followed by a 7-day exposure to Microcystin-LR) notably mitigated hepatic pathologies in mice of the experimental group. The αLA administration led to a significant elevation in the activities of superoxide dismutase, glutathione peroxidase, *etc.* Consequently, αLA was regarded as a promising therapeutic substance for the amelioration of liver oxidative damage after microcystin-LR exposure [154].

The hepatoprotective effect of αLA was experimentally confirmed in a model of liver injury in rats caused by valproic acid, which is prescribed in the treatment of epilepsy [155]. αLA (200 mg/kg for 9 weeks) attenuated fluoride-induced liver damage in mice [156] by inhibiting ferroptosis. Khalaf *et al.* [157] revealed that exogenous αLA (100 mg/kg body weight) supplementation as a hepatoprotective drug in amelioration of intoxication caused by copper nanoparticles in rats. Sadek *et al.* [158] revealed the hepatoprotective effects of αLA against CCl_4-induced liver fibrosis in rats. It reduced the collagen deposition and oxidative stress in the liver as well as downregulated the expression of proinflammatory cytokines, inducible nitric oxide synthase and nuclear factor-kappa B [158].

Since radiation is used in the treatment of cancer, it can cause serious liver toxicity [159]. Recent experimental studies demonstrated that αLA possesses protective effects against the unwanted influences of radiation used in many cancer treatments causing liver damage [159].

As it was concluded recently [160], the occurrence of NAFLD is closely associated with T2DM. It was revealed that orally administered αLA (200 mg/kg body weight) significantly decreased hepatic levels of NLRP3 inflammasome activation-related proteins of interleukin-1β expression by 24.5% in diabetic rats. The authors suggested that αLA might be used as a health dietetic supplement for the alleviation of NAFLD progression associated with T2DM.

It could be concluded that αLA has a lot of protective properties including improvement antioxidant systems, reducing inflammation and stimulatung production of glutathione, which can prevent liver oxidative damage.

4.6. Cancer

In the last decades, researchers have focused their attention on finding natural anticancer drug substances. Among them is a generation, which contributes to αLA-dependent cell death, triggering the mitochondrial pathway of apoptosis in cancer cells, reducing the matrix metalloproteinase activity, decreasing cell motility, invasion and migration, reducing cell viability inducing apoptosis by different mechanisms [128]. In addition, p53 is not necessary for αLA-induced growth inhibition and death of the HCT116 colorectal cancer cells [35]. αLA triggers the mitochondrial pathway of apoptosis and impairs oncogenic signaling. Therefore, it displays anti-metastatic potential.

ROS modulation was considered to be a promising strategy to selectively kill cancer cells [161]. Antioxidants were reported to be useful in the prevention and treatment of cancer *in vitro* and *in vivo* because of provoking apoptosis, inhibition of proliferation and regulation of redox potential in cells [161-163]. For instance, the αLA treatment inhibits cancer metastasis of MDA-MB-231 cells, a human breast cancer cell line, due to the decrease in the levels of metalloproteinases. The treatment with doses of more than 250 μmol/L of αLA reduced the motility of MDA-MB-231 cells [162].

Experimental studies have confirmed the antitumor activity of αLA in various types of cancer [164, 165]. Puksaka *et al.* [164] suggested that αLA affects the structure of β1 and β3 cellular integrins in cancer cells due to its ability to change the status of ROS cells to apoptosis by modulating the redox status of cells, which increases the sensitivity of cancer cells [164]. It also activates monophosphate-activated protein kinase and delays the transforming growth factor-β pathway. Jeon *et al.* [165] conducted studies on the effect of αLA on the proliferation, migration and invasion of thyroid cancer cells. As a result of the study, it was proposed to use αLA for the treatment of thyroid cancer as an adjuvant therapy along with other therapeutic agents. αLA has been also reported to reduce the viability of breast cancer, and colon cancer [166]. This implies that ALA should be used synergistically with other anticancer drugs to reduce the proliferation rate and counteract the effects of the generated ROS.

When there is an oncogenic transformation of human cells, it often results in the production of excessive ROS which have been directly linked to increased proliferation in cancer cells [167, 168]. The targeted elimination of ROS with diets or therapeutic antioxidants reduces the rate of development of certain types of cancers [168].

αLA content within the body reduces essentially with age that further can lead to endothelial dysfunction [11, 169]. The clinical trials involved 120 patients with polycystic ovaries syndrome, which were studied during 3 months of treatment in pioglitazone (30 mg/-time, 1 time/day), αLA (600 mg/time, 1 time/day), and combinative (pioglitazone 30 mg/ day and αLA, 600 mg/day) groups [170]. αLA was regarded as an effective complementary therapy for coping polycystic ovary syndrome due to enhancing glycemic, lipid, and hormonal parameters caused by oxidative stress [171]. αLA synergizes with some antineoplastic drugs in colorectal cancer due to the ability to target p53 for proteasomal degradation [172].

It was concluded that complex treatment with pioglitazone and αLA did demonstrate a better therapeutic effect than any monotherapy alone regarding the hormonal profile [170]. As it was indicated by Önder *et al.* [2024], αLA suppressed the metastasis of ovarian cancer cells by regulating epithelial-mesenchymal transition in the SKOV-3 ovarian adenocarcinoma cell line.

The anticancer activity of αLA was seen in the neuroblastoma cell lines Neuro-2a, Kelly, SK-N-SH and the breast carcinoma cell line SkBr3 as it can significantly decrease cell viability in all four cell lines. One of the possible mechanisms of anticancer activity is a dose-dependent increase of the apoptosis marker Caspase-3 [173]. The significant anticancer potential of αLA and ascorbic acid developed in the liposomal forms has been demonstrated by Attia *et al.* [161]. They [161] concluded that entrapping such antioxidants as ascorbic acid and αLA in nanocarriers (liposomes) may overcome the drawbacks of the low delivery capacity in cancer treatment.

Thus, αLA exhibits cytotoxic and antiproliferative activities on some types of cancer due to the targeted elimination of ROS.

4.7. Infertility

Infertility is a global health item that concerns female or male factors with limitations in the treatment [174]. Oxidative stress, caused by a disrupted balance between ROS and antioxidants, has an impact on the reproductive lifespan of men and women [175, 176] and contributes significantly to the pathogenesis of male in-

fertility and recurrent pregnancy loss due to increased sperm DNA damage [177, 178]. Outcomes of oxidative stress diminish sperm motility, viability and DNA integrity [179].

Varicocele (surgical or non-surgical) has a high incidence among etiological factors of male infertility [177]. Antioxidant supplementation possesses a beneficial impact on seminal oxidative stress, sperm DNA damage and chromatin integrity [177]. αLA has been used in clinical practice to improve the quality of sperm [177]. Therefore, the administration of antioxidants as a potential therapeutic approach is of great scientific and clinical importance for couple infertility [11, 80, 175, 176, 180].

Preclinical studies demonstrate that αLA administration (100 mg daily, oral gavage for 42 days) in rats with primary ovarian failure, induced by 4-vinylcyclohexene diepoxide, possessed a beneficial impact on alleviating ovarian damage. It was confirmed by histological, immunohistochemical, hormone level and oxidative stress markers (caspase-3 immunoreactivity, eNOS immunoreactivity, levels of estradiol, MDA, glutathione, *etc.*) [181]. Another preclinical study revealed the efficacy of combined oral αLA (25 mg/kg) and omega-3 fatty (400 mg/kg) acids treatment during 30 days against cyclophosphamide-induced ovarian toxicity in rats resulted in the prevention of oxidative injury to the ovaries, normalization of the estrous cycle, amelioration of the hormonal status and histological structure of the follicles [182].

αLA at the dose of 50 mg/kg *per os* ameliorates radiation-mediated spermatogenesis defects and testicular fibrosis in male rats *via* suppression of oxidative stress/NF-kB/TGF-β signaling. It improved histological and ultrastructural changes of disorganized seminiferous tubules and decreased interleukin (IL)-6 and cyclooxygenase-2 expression in irradiated rats [183]. The protective impact of αLA, due to antioxidant, anti-inflammatory and related properties, on sperm functions in rodent models for male infertility has been recently reviewed. αLA treatment restored the testicular architecture, reproductive performance and sperm parameters, significantly reduced the DNA damage, modulated androgenesis and steroidogenesis, and maintained redox and immune system homeostasis in rodents [184].

The clinical trial revealed that an 80-day administration of αLA at a daily dose of 600 mg after varicocelectomy in infertile men statistically significantly enhanced sperm motility, compared with the placebo group that had undergone microsurgical repair [185]. Another clinical trial with a similar research design of αLA supplementation showed alleviation of sperm oxidative stress, DNA damage and chromatin integrity in men with high sperm DNA injury [177].

The analysis of couples with recurrent pregnancy loss demonstrated that a treatment course by αLA (600 mg/day for 80 days) reduced sperm DNA injury and lipid peroxidation while boosting sperm total motility and chromatin compaction in the male partners. The rate of spontaneous pregnancy in the αLA group exceeded the placebo group [178].

The beneficial impact of αLA in oocyte maturation, fertilization, embryo development, and reproductive outcomes has been found in clinical studies. Regular supplementation with αLA led to a reduction of pelvic aches in endometriosis, regularized menstrual flow and metabolic ailments, and improved sperm quality [175]. αLA supplementation (300 mg twice a day for 90 days) in primary infertile males, complaining of idiopathic asthenozoospermia, ameliorated sperm quality (total and progressive motilities) and viability, and a statistically significant increase in semen volume and sperm concentration has been demonstrated. Sperm parameters and functional tests were enhanced, while abnormal morphology was reduced significantly [186]. αLA treatment alone and combined with N-acetyl-cysteine developed beneficial effects on the structural and functional properties of cryopreserved asthenoteratozoospermia patients' sperm, improving sperm motility, viability and DNA fragmentation and significantly increasing the mitochondrial membrane potential [187, 188]. The oral administration of αLA improves normal sperm forms, sperm concentration, and its total and progressive motility, compared with other modes of treatment; αLA also significantly enhances semen volumes [174].

The combination therapy with αLA (1500 mg/day) and metformin (1800 mg/day) moderated the complications of polycystic ovary syndrome and subsequently raised oocyte and embryo quality in women undergoing intracytoplasmic sperm injection; the MDA, fasting blood sugar, insulin, luteinizing hormone, LH/follicle-stimulating hormone levels reduced significantly and the total antioxidant capacity elevated significantly, compared with the metformin group [187].

Combined therapy by αLA and myo-inositol leads to significantly higher enhancement of the oxidative status in oocytes of infertile obese women, who were additionally to folic acid (400 mg daily) supplemented with αLA (800 mg) and myoinositol (2000 mg) for 2 months before ovarian stimulation [180]. 12-week course of treatment by αLA, combined with Chinese herbal formulation Jujing Decoction, in patients with

asthenospermia and teratospermia significantly improved sperm motility, decreased morphologically abnormal sperm and sperm DNA fragment index, elevated the pregnancy rate and achieved a high clinical safety and overall effectiveness rate, compared with the blank control group [189].

The αLA addition resulted in amelioration of sperm motility, declined DNA damage and lipid peroxidation. Such properties might be used for sperm cryopreservation of male gametes in assisted reproduction technologies [179]. Supplementation of freezing media with αLA (0.02 and 0.5 mM) in the cryopreservation of semen samples, received from infertile asthenoteratozoospermic men, developed a significant protective effect against cryodamage by preserving the sperm structural and functional characters. The effective concentrations of αLA significantly raised motility and viability, lessened DNA fragmentation, oxidative stress level and apoptosis protected the acrosome integrity [190].

in silico approach has been used [191] to evaluate possible therapeutic targets and mechanisms of αLA action on primary ovarian insufficiency. The researchers have identified 152 potential therapeutic targets and pathway mechanisms for αLA in the treatment of primary ovarian insufficiency.

This subsection data of *in vitro*, *iv vivo*, clinical, and *in silico* studies reveal beneficial health effects of αLA, which might be mainly attributed to its antioxidant and anti-inflammatory activities. It opens new possibilities for a wider recommendation of αLA to improve the sperm's structural and functional characteristics in cases of male and female infertility, varicocele, primary ovarian insufficiency, recurrent pregnancy loss and related health conditions.

4.8. Nephropathy

Kidneys are an important detoxifying organ that eliminates metabolic waste. Renal cells are involved in the regulation of blood pressure, maintenance of electrolyte balance, blood pH homeostasis, erythropoiesis and vitamin D synthesis. Their diminished function can lead to the development of either acute kidney injury or chronic kidney disease [192]. Kidneys are especially vulnerable to oxidative stress, which might be a contributing factor in the pathogenesis of renal disorders [193].

The numerous *in vivo*, clinical, cell culture and *in silico* investigations demonstrate the beneficial nephroprotective effects of αLA, used alone or in combined therapy. The following pharmacological effects are related to the nephroprotective impact of αLA: antioxidant, anti-inflammatory, antidiabetic, metal chelating and detoxifying [194]. Antioxidant potential and scavenging activity of αLA, due to its redox properties, provide a protective impact on cells against oxidative stress, since it directly scavenges ROS and RNS [194, 195]. The significance of αLA in the prevention and treatment of kidney ailments has been recently confirmed [192].

Preclinical studies demonstrated that treatment with the αLA-enriched diet for 60 days prevented intermittent hypoxia-induced renal damage in mice. It has been revealed in a mouse model of sleep apnea that the treated animals had reduced levels of plasma and renal oxidative stress and inflammation (TNF-α), compared with hypoxia-exposed mice. αLA lowered kidney cellular apoptosis and tubular damage; it also weakened glomerular hypertrophy and elevated albuminuria [196].

The nephroprotective effect o/f αLA against oxidative kidney injury induced by iron overload (40 mg/kg iron sucrose administration followed by 100 mg/kg αLA for 28 days) in male rats has been studied [197]. Under conditions of such iron overload, αLA significantly decreased MDA level and accelerated superoxide dismutase activity in the kidney tissue as well as suppressed the activation of p38 MAPK [197]. Later, the efficacy of the same αLA dose against the higher concentration of iron sucrose (80 mg/kg) was also investigated [198]. It was revealed that the renoprotective effect might be implemented through the following mechanisms: suppression of the mRNA expression of the kidney isoform of NADPH oxidase and TNF-α, and reduction of caspase-3 protein expression.

Administration of αLA decreased renal damage in the streptozotocin-induced adult diabetic male rats. The αLA diabetic group demonstrated a higher renoprotective impact on renal histopathology than the group treated by α-tocopherol [199]. The nephroprotective effect has been investigated in adult male rats receiving αLA treatment (100 mg/kg, for 6 weeks) after exposure to insecticide diazinon (40 mg/kg). The nephrotoxic impact of diazinon is caused by alterations of extracellular matrix proportion, inhibiting cholinesterase and oxidative stress. αLA enhanced the distribution of laminin and fibronectin in the kidney tubules and exhibited hypoazotemic effect, significantly lowering urea and creatinine levels [200]. αLA in a dose of 60 mg/kg (intravenously) possessed significant antioxidant and anti-inflammatory effects, downregulating the expression of pro-inflammatory cytokines in rat kidney tissue against lipopolysaccharide-induced oxida-

tive stress. αLA impaired kidney edema status [193]. αLA, administered orally 60 mg/kg/day for 6 weeks in male rats with T2DM, induced by nicotinamide and streptozotocin, protected against the development and progression of diabetic kidney disease by activating renal CSE/H2S pathway.

Dugbartey *et al.* [201] found that αLA administration ameliorated antioxidant status and lipid profile as well as decreased inflammation in diabetic rodents. αLA treatment improved the function of pancreatic beta cells, normal insulinemia, normoglycemia and the level of triglycerides, and averted kidney injury. Compared with the diabetic control group, the administration of ALA resulted in the prevention of increased levels of serum and tissue MDA, collagen deposition, α-SMA expression, apoptosis and serum IL-1β and IL-6 levels, concurrently glutathione content in kidney tissue and plasma HDL-C were significantly elevated [202].

Renoprotective effects of αLA (100 mg/kg, 10 days) were demonstrated by Oktan *et al.* [203] against nephrotoxicity in rats, developed by antibiotic colistin. αLA treatment resulted in the decrease of oxidative stress and kidney tubular apoptosis, due to NADPH oxidase 4 and caspase-3 suppression. αLA also impaired mRNA expression of kidney injury molecule-1, Nox4 and p22phox in the renal tissue, and kidney active caspase-3 protein expression [203]. Prevailing mechanisms of αLA nephroprotective effect in several animal models of kidney damage, were investigated by different research groups, such as elevation of antioxidant capacity, prevention of inflammation, kidney fibrosis mitigation, and reduction of nephron cell death [192].

The αLA therapy prevented diabetic nephropathy by attenuation of hyperglycemia, albuminuria, the loss of kidney function, growth of the mesangial matrix, and the development of glomerulosclerosis in diabetic rats [195]. The αLA treatment at the daily 20 mg/kg for 8 weeks resulted in a hypoazotemic effect, reducing the blood urea nitrogen and serum creatinine. It ameliorated the histopathological profile by the reduction of glomerular and mesangial cellular injury in diabetic rats, as well as lowered the levels of MDA and improved activity of the superoxide dismutase [195].

An interventional clinical trial that involved 59 patients with autosomal dominant polycystic kidney disease, demonstrated that 3- and 6-month uses of αLA at a daily dose of 1600 mg significantly lowered serum glucose, insulin, insulin resistance and serum uric acid; a significant increase in bicarbonates level and flow--mediated dilation, and a significant decrease of C-reactive protein and renal resistive index have also been detected [204].

Another report of clinical cases showed that pediatric patients with cystinuria, who received regular doses of αLA in addition to conventional therapy with potassium citrate, had no adverse effects and a 2-month course contributed to the disappearance of renal stones in one patient. αLA enhanced markers of cystine solubility in urine with elevated cystine capacity and lowered cystine supersaturation without any changes in cystine excretion or urine pH [205]. The αLA therapy lowered 24h urine albumin excretion rate and urine albumin to creatinine ratio in patients with diabetic nephropathy, which is generally characterized by raised urine albumin excretion rate and lowered glomerular filtration rate [206]. Outcomes of the clinical trial involving 102 patients with early-stage diabetic kidney disease, revealed that a 14-day αLA course, combined with valsartan, diminished the level of inflammatory cytokines in serum and ameliorated kidney function, significantly decreasing hypersensitive C-reactive protein, TNF-α, urinary albumin excretion rate, β2-microglobulin and cystatin C, compared with the group administered valsartan alone [207]. Combined treatment with valsartan, amlodipine and αLA exhibited a potent protective effect on patients with diabetic nephropathy, due to its significant impact on total antioxidant capacity, IL-6 and β2-MG levels [208].

Combined therapy with αLA and alprostadil of 76 patients with senile diabetic nephropathy ameliorated the effectiveness rate compared with alprostadil monotherapy and decreased the blood glucose. An improvement in kidney function is related to the effective reduction in patients' serum of chemerin and neutrophil gelatinase-associated lipocalin levels [209]. In patients with diabetic nephropathy, the combined administration of αLA (800 mg) and pyridoxine (80 mg) for 12 weeks significantly diminished albuminuria through the decline of the oxidative stress, advanced glycation end-products and systolic arterial pressure [195]. The study of Zhang *et al.* [210] examined the effects of αLA treatment on chemerin-treated human mesangial cells. αLA reversed the effects of chemerin, inhibited HMCs proliferation and lowered IL-6, TNF-α, NF-κB p-p65 and TGF-β expression. Recent *in silico* study demonstrated that αLA is a promising drug candidate for acute renal failure, due to its ability to reduce a cardiorenal syndrome type 3, which is a frequent cardiac complication in such patients [211].

Generally, numerous experimental and clinical studies demonstrated significant healing effects of αLA attributed mainly to its antioxidant and antimicrobial properties.

4.9. Skin Aging

External manifestations of oxidative stress are noticeable in the condition of the skin, it becomes dry and wrinkles appear. Also, there are pathological changes in the body associated with a violation of the barrier functions of the skin [65]. This disrupts the barrier function of the skin and, as a result, increases the risk of skin diseases. Exogenous skin aging is associated with exposure to various environmental factors (high or low air temperature, wind, polluted air with toxins, solar ultraviolet and infrared rays, and nicotine). Several other factors also affect the rate of aging; for example, poor-quality nutrition, low physical activity, stress, contact with chemicals, and the use of excessive amounts of detergents in the home. Skin aging is also influenced by individual characteristics of the immune system and neuro-humoral regulation of the body, as well as genetic diseases [212-214].

Endogenous skin aging occurs at the cellular level, affecting keratinocytes, fibroblasts, and melanocytes. It should be noted that αLA has a positive effect on the composition of the skin, regulates the passage of water and nutrients through the cells of the epidermis, and protects the epidermal barrier from the penetration of bacteria and viruses. These processes in cells prevent premature aging [215].

The protective properties of αLA (100 mg/kg) had a favorable effect on skin fibrosis in the bleomycin-induced scleroderma model in mice [216]. It was revealed that αLA injected intraperitoneally twice a week for 21 days was able to reduce dermal thickness, inflammation score and expression of TNF-α in the skin. Therefore, it was regarded as a promising agent for the treatment of skin fibrosis in patients with scleroderma [216].+

As it is known, collagen is one of the major constituents of the skin and age-related changes in collagen such as increased level of glycation, a reduction in collagen quantity, and an increased rate of collagen oxidation have been documented. In an animal model of accelerated aging, mice were fed with fructose [217]. This feeding increased the collagen crosslinking in the skin, enhanced the plasma levels of glycated hemoglobin, and changed the collagen solubility [217]. αLA administration significantly improved the collagen quality and thwarted collagen deterioration. The present study demonstrated that skin aging might be managed by αLA supplementation [217].

Alopecia induced by chemotherapy has a significant impact on quality of life. Aiba *et al.* [218] conducted the *in vivo* study and concluded that cooling therapy and αLA administration significantly facilitated recovery from experimental chemotherapy-induced alopecia (model of cyclophosphamide, 120 μg/g) through decreasing vascular permeability. Another study found that αLA improved basal skin perfusion, endothelial function, skin sensory sensitivity, and age-related modifications in skin resistance to low pressures by delaying the reduction in cutaneous blood flow from baseline for increased crushing pressure [219].

The availability of any active substance through the skin depends on its release from the vehicle and the subsequent permeation through the dermal layers [220]. It was demonstrated that rheological features, such as thixotropy, viscosity, and compliance, strongly influenced the release of αLA from the emulsion.

αLA is as usual administered by oral route or injection and is rarely used topically *via* skin because of its bad penetration. Kubota *et al.* [221] developed a novel nanocapsule of αLA with a non-ionic surfactant to improve skin permeability. Their findings suggested that nanoencapsulation of αLA was very effective for topical application.

Sherif *et al.* [222] found that topical 5% αLA application was quite effective in the treatment of photo-damaged skin. It was found that the developed gel loaded with αLA cubosomes provided a lower release rate than another one loaded with the unencapsulated αLA. The conducted clinical study evaluated the efficacy of an anti-wrinkle gel and the volunteer's satisfaction upon the application of gel loaded with αLA cubosomes topically. It indicated almost complete resolution of fine lines in the upper lip area and the periorbital region as well as overall improvement in skin texture in most subjects [222].

Skin aging is closely related to redox imbalance caused by UV radiation exposure [223]. The co-nanoencapsulation αLA and resveratrol with an average particle diameter close to 200 nm improved their antioxidant properties [223]. Such a nanoformulation increased the stability of substances under storage as well as photostability under UV light exposure along with their controlling release.

Therefore, αLA could be regarded as a potential bioactive compound in pharmaceutical and cosmetic fields for use to inhibit age-associated consequences of oxidative damage in dermatology [224].

Some examples of recent clinical trials that have been investigating the therapeutic effects of αLA in age-related conditions are presented in Table **1**.

Table 1. Examples of completed clinical trials regarding therapeutic potential of αLA in age-related disorders (from ClinicalTrials.gov).

Official Title	Location	Condition	Protocol (Study Type)	Number of Subjects(Ages Eligible for Study)	Intervention/ Treatment	ClinicalTrials.gov ID	References
Evaluation of the Safety, Tolerability and Impact on Biomarkers of Anti-Oxidant Treatment of Mild to Moderate Alzheimer's Disease Conditions	Arizona and California, United States	Alzheimer's Disease	Interventional (Phase 1)	75 (60-85 years)	Drug: Vitamin E, Vitamin C, and αLA	NCT00117403	[225]
Fish Oil and Alpha Lipoic Acid in Mild Alzheimer's Disease	Portland, Oregon, United States	Alzheimer's Disease	Interventional (Phases 1/2)	39 (55 Years and older)	Dietary Supplements: Fish Oil and αLA	NCT00090402	[226]
Lipoic Acid and Omega-3 Fatty Acids in Alzheimer's Disease	Portland, Oregon, United States	Alzheimer's Disease	Interventional (Phases 1/ 2)	67 (55 Years and older)	Drug: αLA and fish oil concentrate	NCT01058941	[227]
An Open-label Trial of Alpha-lipoic Acid/L-acetyl Carnitine for Progressive Supranuclear Palsy (PSP): Effect Upon Oxidative Damage and Mitochondrial Biomarkers	New York, New York, United States	Neurodegenerative illness (progressive supranuclear palsy)	Interventional (Phases 1/2)	11 (40 Years to 75 Years)	Drug: αLA and L-acetyl carnitine	NCT01537549	[228]
Evaluation of Efficacy and Safety of add-on Alpha-lipoic Acid on Migraine Prophylaxis in Adolescent Population ClinicalTrials.gov	Bhubaneswar. India	Migraine	Interventional (phase 4)	60 (10 Years to 19 Years)	Drug: Flunarizine 5mg Drug: αLA 300mg	NCT04064814	[229]
The Association of Alpha Lipoic Acid to the Median Nerve Decompression in the Carpal Tunnel Syndrome: a Randomized Controlled Trial	Bologna, Italy	Neuropathy (Carpal Tunel Syndrome)	Interventional (phase 4)	64 (18 Years to 80 Years)	Dietary Supplement: αLA post median nerve decompression	NCT01895621	[230]
Dose Finding and Tolerability Study of Alpha-lipoic Acid in Patients at Risk for Paclitaxel Induced Peripheral Neuropathy	Chicago, Illinois, United States	Peripheral neuropathy	Interventional (Phases 1/2)	9 (18 Years and older)	Drug: αLA	NCT01313117	[231]
Effect of Alpha Lipoic Acid on Obesity Related Comorbidities	Urumqi, Xinjiang, China	Metabolic disorders (T2DM, obesity, cardio-vascular disease)	Interventional (phases 2/3)	70 (18 Years to 60 Years)	Dietary Supplement: αLA	NCT00994513	[232]

(Table 1) contd....

Official Title	Location	Condition	Protocol (Study Type)	Number of Subjects(Ages Eligible for Study)	Intervention/ Treatment	ClinicalTrials.gov ID	References
Exploratory Study of Lipoic Acid Supplementation on Oxidative Stress, Inflammatory and Functional Markers in Asthmatic Patients	GuadαLAjara, Mexico	Asthma	Interventional (phase not applicable)	55 (18 Years to 75 Years)	Dietary Supplement: αLA	NCT01221350	[233]
Alpha-lipoic Acid Reduces Left Ventricular Mass in Normotensive Type 2 Diabetic Patients With Coronary Artery Disease	Wuhan, Hubei, China	Coronary Artery Disease, Left Ventricular Mass, Type 2 Diabetes	Interventional (phase 4)	66 (40 Years to 70 Years)	Drug: αLA	NCT01877590	[234]
The Effects of Lipoic Acid on Glycaemic Control in Type 2 Diabetes	Livingston, Scotland, United Kingdom	Type 2 Diabetes	Interventional (phase 2)	18 (18 Years and older)	Drug: αLA	NCT00398892	[235]
Alpha Lipoic Acid and Diabetes Mellitus: Potential Effects on Peripheral Neuropathy and Different Metabolic Parameters	Banhā, Qalubiya, Egypt	Diabetic pouneuropathy, Type 2 Diabetes	Interventional (phase not applicable)	90 (16 Years and older)	Drug: αLA	NCT04322240	[236]
Alpha Lipoic Acid in the Treatment of Diabetic Retinopathy	Munich, Germany	Diabetic Retinopathy	Interventional (phase 3)	52 (45 Years to 68 Years	Drug: αLA	NCT01208948	[237]
Alpha Lipoic Acid and Polycystic Ovary Syndrome	San Francisco, California, United States	Polycystic Ovary Syndrome	Interventional (phase 4)	22 (18 Years to 50 Years)	Dietary Supplement: αLA	NCT00505427	[238]
The Effect of α-lipoic Acid Treatment in Patient With Cardiac Autonomic Neuropathy (CANON)	Seoul, Korea, Republic of	Type 2 Diabetes Cardiac Autonomic Neuropathy	Interventional (phase 4)	91 (20 Years to 80 Years)	Drug: αLA	NCT02056366	[239]
Role of Alpha-Lipoic Acid Against Chemotherapy Induced Toxicities in Breast Cancer Patients	Tanta, Gharbia, Egypt	Breast cancer	Interventional (phase not applicable)	64 (18 Years to 70 Years)	Dietary Supplement: αLA and chemotherapy	NCT03908528	[240]

Some researchers published the results of their clinical trials. Thus, Shinto *et al.* [241] concluded [226] that the combination of omega-3 fatty acids and αLA over 12 months was able to slow the cognitive decline in patients with Alzheimer's disease. A randomized clinical trial conducted with 60 adolescent migraineurs [229] revealed that αLA was an effective nutraceutical for migraine prophylaxis [242]. After finishing clinical studies [240], Werida *et al.* [243] concluded that αLA in a dose of 600 mg/day for 6 months may represent a promising adjuvant therapy in attenuating chemotherapy-induced toxicities (doxorubicin-induced cardiotoxicity and paclitaxel-associated neuropathy) in women with breast cancer. The participation of αLA was suggested in cell growth and differentiation [244] Recently, αLA demonstrated the ability to reprogram metabolism [17]. This fact could be crucial to clinical practice.

Thus, numerous *in vitro, in vivo* and clinical research works proved efficiency of αLA-containing drugs in health issues, in which pro- and antioxidant balance has been disrupted (neurodegenerative diseases, diabetes, immune disorders, tumors, *etc.*). The efficiency of αLA attributes to its unique antioxidant properties and noticaeble effect on the concentrations of reduced forms of other antioxidants. Therefore, αLA ws called 'an antioxidant of antioxidants' [244]. Correction of the immunological status of the human body can be attributed to one of the promising areas of studying the biological activity of αLA.

5. INVESTIGATIONS OF THE ALA EFFECTS IN VARIOUS DOSAGE FORMS AND ITS SAFETY

Food supplements make up a primary source of αLA intake, ranging from 50 to 1200 mg per day in different studies [12, 84, 87]. αLA is currently accessible as a dietary supplement mainly in tablet and capsule forms [245]. The clinical trials revealed that patients who were treated both intravenously and then orally with αLA felt much better regarding neuropathic pain syndrome compared to those who received only oral αLA [246].

As the bioavailability of αLA in its pure form is low (approximately 30%), and developing nanoformulations have shown promise in this regard [11]. Nanodelivering could be regarded as a promising direction to improve the antioxidant effect of αLA as it enhances its bioavailability by providing an efficient targeted delivery in more appropriate dosing. A new αLA nanocapsule that is water-soluble, 8-15 nm in diameter, and made as αLA micelles was also developed to increase skin permeability. *in vivo* tests revealed that this formulation is very effective at reducing the effects of UV-induced pigmentation and epidermis thickening for local use [221].

Due to the low half-life of αLA and its instability under stomach-like conditions, it was nanoencapsulated into chitosan (average diameter of 44 nm) [247]. The developed nanocarriers with αLA demonstrated high antioxidant activity and stability under such a condition for up to 3 h in the *in vitro* experiments. The research which improved the photo-stability of αLA-loaded nanostructured lipid carriers was conducted by Wang *et al.* [248]. A new natural nanodrug was developed with ascorbic acid and αLA cross-linked vesicles [249]. Such an integration greatly increased the blood half-life of these antioxidants in mice and amplified the antioxidation capacity through the mutual recycling of two redox pairs αLA/DHLA and ascorbic acid/αLA. This nanoformulation decreased the apolipoprotein E-deficient mice's plaque area (from 52% to 13%), which was much lower than those of free αLA (≈38%) and ascorbic acid (≈45%) [249]. The applications of various αLA and poly-αLA-derived-biomaterials were summarized by Lv *et al.* [81] with an emphasis on their use for designing new biomaterials with diverse therapeutic properties.

Recently, Calabrese *et al.* [250] revealed the underlying mechanisms that mediated the αLA-induced hormetic effects in biphasic dose response due to the induction of low levels of ROS that activate key cell signaling antioxidant pathways. The hormetic effects are linked to reducing the progression of neurodegenerative diseases and preserving sperm functionality during cryopreservation [250].

The findings of the *in vitro* penetration experiment introduced a novel approach for investigating emulsions using an ionic liquid strategy for transdermal delivery of αLA, showed outstanding anti-aging efficacy, and were crucial for the creation of topical preparations [251].

The retrospective observational research showed a decrease in total cholesterol, low-density lipoprotein-cholesterol, triglycerides, and fasting plasma glucose in the groups that received αLA at doses of 800 and 1200 mg/day, compared to those obtained with alpha-lipoic acid 400 mg/day [252]. Another trial investigation of 500 mg/day oral αLA in individuals with T2DM showed substantial reductions in HbA1c, C-reactive protein, fasting plasma glucose, and a linear drop in body weight at doses greater than 600 mg/day [253]. One more clinical study found that diabetic patients on hemodialysis who got 600 mg of αLA once daily in addition to their main treatment had lower levels of C-reactive protein, TNF-α and higher Hb concentrations than the control group [254]. A randomized clinical trial in which subjects with neuropathic pain were given the dietary supplement αLA orally for two months at doses of 400 mg/day or 800 mg/day showed significant reductions in pain [255].

Regarding αLA safety, it should be noted that the experimental research concluded that αLA may exert both anti- and prooxidant effects, depending on the current physiological and metabolic state of the tested organisms as well as the tested doses [256]. Thus, while αLA has a renoprotective effect in diabetic nephropathy, it may demonstrate the potential harmful influences on a healthy kidney. Its common daily dose ranges from 100 to 600 mg once or twice a day, and is usually well tolerated. However, at higher doses, adverse effects can include disorientation, seizures, lactic

acidosis, rhabdomyolysis, and multiple organ failure, which can be deadly, have been documented following a single dosage [257, 258]. According to reports describing the safety profile of αLA-containing dietary supplements, the most often reported adverse reactions were cutaneous, immunological, liver disturbances, and autoimmune syndrome [102, 259, 260].

αLA is generally considered safe when taken in appropriate doses, however, there are certain contraindications and precautions: liver disease, combined with medications for diabetes (*e.g.*, insulin or oral hypoglycemic drugs) may enhance the effects and potentially lead to hypoglycemia, thiamine deficiency, thyroid problem, and αLA should be discontinued immediately if an allergic reaction occurs. Regarding the safety during pregnancy and breastfeeding, there is insufficient evidence [202, 258, 261]. Therefore, the use of αLA may reduce symptoms of many health disorders and provide a safe, acceptable, and efficient strategy for treatment however, it requires risk-benefit analysis and ongoing safety profile monitoring.

CONCLUSION

αLA can be considered a powerful antioxidant with anti-aging properties. This molecule has the unique property of being able to penetrate both hydrophobic and hydrophilic environments, making it an efficient scavenger of free radicals in various cellular compartments. Being both the endogenous and dietary agent, αLA is a potent antioxidant and anti-aging molecule that has a wide range of possible applications in the management of various health conditions. The complex of αLA/DHLA has the power to recycle endogenous antioxidants. They improve mitochondrial function and regulate the expression of genes involved in aging and oxidative stress.

A huge number of experimental and clinical studies highlight the effectiveness of αLA as a therapeutic component for different age-related disorders. αLA has a powerful neuroprotective effect and helps to improve cognitive parameters. αLA is widely used for the prevention and treatment of diabetes and other metabolic disorders due to normalizing fat metabolism and blood cholesterol levels. It has a protective effect on liver cells and helps to eliminate toxins and heavy metals from the body. Different cancers, skin senescence, nephropathy, and infertility could be also coped with αLA supplementations. The ability of αLA to correct the immunological status and reprogram overall metabolism makes it a promising molecule with a wide range of potential applications in the field of medicine. Nanoencapsulation enhances the bioavailability of αLA and provides targeted delivery that results in more efficient dosing. However, further research, including large-scale clinical trials, is needed to fully understand its effectiveness, optimal dosage, safety and long-term effects.

LIST OF ABBREVIATIONS

ROS	=	Reactive Oxygen Species
DHLA	=	Dihydrolipoic Acid
C6	=	Chiral Center
T2DM	=	Type 2 Diabetes Mellitus

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