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Review Article

THERAPEUTIC USE OF ALPHA-LIPOIC ACID SUPPLEMENTATION: A REVIEW ON CURRENT USE AND FUTURE PROSPECTIVE

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ABSTRACT

Alpha-lipoic acid (ALA, thioctic acid, 5-(1,2-dithiolan-3-yl) pentanoic acid) is an organosulfur compound produced by plants, humans, and animals. ALA plays a crucial role in mitochondrial bioenergetics reactions. It is a natural antioxidant and a dithiol compound. ALA is a coenzyme that plays a crucial role in the function of pyruvate and Alpha-ketoglutarate dehydrogenase complexes found in mitochondria. ALA has cytotoxic and antiproliferative effects on several cancers, including Polycystic Ovarian Syndrome (PCOS). Most of ALA's clinical applications come from its antioxidant properties, but it also shows potential in treating female and male infertility. Although ALA can potentially be a therapeutic agent, its pharmacokinetic profile limits its effectiveness. Research suggests that ALA has a short half-life and low bioavailability (around 30%) because it gets broken down in the liver, has reduced solubility, and is unstable in the stomach. Liquid formulations have higher bioavailability and plasma concentration than solid dose forms. This review covers the current clinical evidence on using ALA to prevent, manage, and cure numerous disorders, including diabetic neuropathy, obesity, central nervous system-related ailments, and pregnancy abnormalities.

Keywords: Alpha-lipoic acid, Bioavailability, Formulations, Pharmacological potential, Thioctic acid

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INTRODUCTION

Alpha-lipoic acid (ALA), additionally referred to as 1,2-dithiolane-3-pentanoic acid or thioctic acid, is a chemical present in mitochondria and required for a variety of enzyme processes. Reed discovered ALA as an acetate-replacing factor in 1951 [1], but its initial therapeutic application was in 1959 for the management of severe poisoning caused by Amanita phalloides, which is commonly referred to as death cap (from mushrooms) [2]. ALA functions as a cofactor in enzyme complexes involved in metabolic activities and the production of energy for cells [3]. The presence of this asymmetrical carbon gives rise to the two distinct forms of ALA, each with its own unique chemical properties and potential biological activities [3]. Both S and R enantiomers are present in equal amounts in ALA. The human body creates a little amount of ALA, but it is inadequate to supply the cell's energy requirements. It comes largely from food, specifically meat and vegetables. This acid can also be found in fruits [4].

As a nutritional supplement, ALA has become a popular element in everyday items such as anti-aging remedies and multivitamin formulas [5]. The use of ALA in nutritional supplements is growing due to its antioxidant and anti-diabetic properties [6]. It also helps with age-related cognitive decline, diabetes, Cardio Vascular Disease (CVD), male reproductive problems, neurological and muscular atrophy, and malignancies [7]. Furthermore, it regulates several inflammatory pathways of signaling [8]. ALA serves several activities (fig. 1). Heavy metals in the circulation cause oxidative stress, whereas ALA, being an excellent antioxidant, removes heavy metals from the bloodstream, preventing oxidative stress (fig. 1). ALA is distinct from other antioxidants due to its amphipathic characteristics as a lipid and water-soluble molecule [9].

On the other hand, ALA possesses various therapeutically useful features [10]. It also effectively eliminates toxic metals from circulation, which cause oxidative stress [5]. The most significant distinguishing feature of ALA from other types of antioxidants is that it interacts as both lipid and water-soluble molecules [5]. It is undeniably a powerful antioxidant, but its usage for therapeutic purposes is illegal for a variety of reasons; yet, it is utilized as a supplementation in particular fields as well as a treatment in another [10-12]. These constraints are caused by some intrinsic properties of the material itself, such as its changeability owing to the disclosure of the dithiolane ring and the formation of bonds of disulfide among molecules. Furthermore, besides its well-known antioxidant properties, ALA serves a variety of additional roles, such as its role in mitochondrial energy production by functioning as a cofactor for several enzymes that regulate metabolism. Numerous cell cultures and animal experiments have demonstrated that ALA and Dihydrolipoic Acid (DHLA) bind redox-active metals. It was discovered that the quality of the chelated metal controls whether ALA and its modified form bind to metal ions [13]. Diabetes Mellitus (DM), high blood pressure, dementia, Alzheimer's disease, Down syndrome, cognitive impairment, and certain forms of cancer, particularly breast cancer, have all been linked to several biological actions of ALA [8]. This review covers the current clinical evidence on using ALA to prevent, manage, and cure numerous disorders, including diabetic neuropathy, obesity, central nervous system-related ailments, and pregnancy abnormalities.

Search strategies

The presented material was gathered from Google Scholar, ScienceDirect, clinicaltrials. gov, and PubMed using the keywords α-lipoic acid, Alpha-lipoic acid, or Alpha lipoic acid [1]. The content in this manuscript is from the 1st January 2019–31st December 2023 year and includes the search terms alpha lipoic acid, obesity, ageing skin, Type 2 Diabetes (T2D), rheumatoid arthritis, vascular disease, asthma, multiple sclerosis, gut microbiota, cancer, neurological disorder, phytochemical properties, metabolic disease, neuroprotective activities, inflammatory, antimicrobial, and polycystic ovarian syndrome.

Pharmacological or therapeutic activities of ALA

ALA has received a lot of attention over the years as a dietary additive that has been shown to help with the treatment and management of a variety of diseases [14]. ALA's pharmacological benefits are mostly connected to its antioxidant activity, which also exhibited noteworthy effects on the cardiovascular system, anti-aging, detoxifying, anti-inflammatory, anti-tumor, and neurologically protective features [15].

Efficacy of ALA in obese or overweight-related disorders

Lifestyle changes in daily exercise and nutrition habits provide the cornerstone of an effective approach to improving metabolic conditions and reducing obesity. ALA exhibits many anti-obesity properties [15]. Based on a clinical trial, ALA supplementation reduces body weight and Body Mass Index (BMI) [16]. The

combination of curcumin and ALA lowers weight gain and obesity. ALA helps regenerate glutathione and vitamins C and E and promotes glutathione synthesis. Hirata disease, or insulin autoimmune syndrome (IAS), is a rare form of autoimmune hypoglycemia characterized by elevated insulin levels and anti-insulin autoantibodies [16]. ALA has lately emerged as a cause of IAS. Furthermore, excellent care is needed to suggest this damage due to α-lipoic acid supplementation [16].

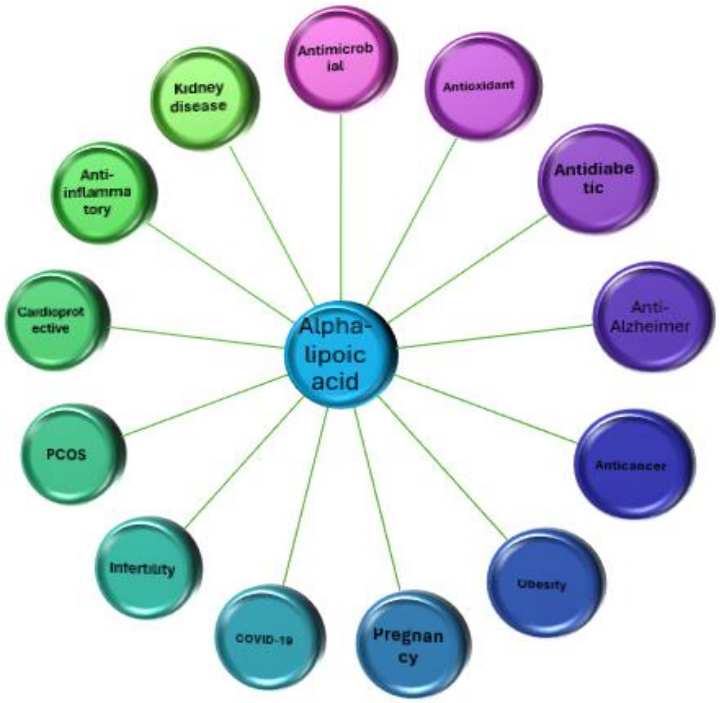

Fig. 1: Clinical effects of alpha-lipoic acids

Table 1: Summary of the therapeutic potential of alpha-lipoic (ALA)

Therapeutic potential	Key effects	References
Obesity or overweight-related disorders	• ALA supplementation reduces body weight and Body mass index (BMI). • The combination of curcumin and ALA lowers weight growth and obesity.	[15, 16]
Antidiabetic as well as diabetic Neuropathy potential	• Possible therapeutic application of ALA in diabetes due to its capacity to increase both blood sugar levels in insulin-sensitive and insulin-resistant muscle tissues. • ALA consumption improved the quality of life of diabetic neuropathy patients while also lowering main warning signs and triglyceride levels.	[17-20]
Antioxidant capabilities	• Assist in regenerating naturally occurring antioxidants including glutathione, vitamins C and E, and repair damage caused by oxidation. • ALA plays a direct role in reducing oxidative stress.	[5, 22, 23]
Neurologically Protective Effects	• The antioxidant property of ALA is associated with its neurorestorative and neuroprotective effects.	[6, 24]
Neurodegeneration	• ALA and omega-3 fatty acids have an additional effect on reducing cognitive deterioration and improving functioning in Alzheimer's disease	[25-27]
Cardiac Disease	• Dihydrolipoic acid (DHLA) has been shown to modulate blood lipids, protect against LDL oxidation, and reduce high blood pressure, demonstrating that ALA may be a preventive agent against cardiovascular illness.	[7]
Pregnancy	• ALA following vaginal administration, its impact on the implementation process (referring to the initial stages of pregnancy where the fertilized egg attaches to the uterine wall), and its efficacy in preventing or inducing preterm birth.	[29]
Renal Related Disease	• High levels of glucose in the blood can lead to damage to the small blood vessels in the kidneys, while hypertension can cause damage to the larger blood vessels and impair kidney function over time. • ALA may have protective effects on the kidneys by mitigating oxidative stress, inflammation, and endothelial dysfunction, which are key factors in the progression of kidney disease.	[30, 32, 33]
Antimicrobial Activity	• ALA demonstrates a diverse array of properties, including antimicrobial, antifungal, antinematodal, and antiviral activities, impacting various targets within the body.	[34]
Inflammatory Disease Potential	• ALA has also been shown to work as a preventive measure against chemotherapy by inhibiting inflammation that is associated with tumorigenesis.	[35]
Polycystic Ovarian Syndrome Potential	• Combined therapy of D-chiro-inositol and ALA may have significant hormonal benefits for women with PCOS	[38]
Infertility	• ALA may increase sperm motility and minimize sperm DNA damage, hence enhancing overall sperm quality. • ALA holds promise as a therapeutic option for addressing infertility, particularly in improving sperm quality.	[43]
COVID-19	• ALA provides protection against SARS-CoV-2 by opening ATP-dependent K+ channels (Na+, K+-ATPase) in the human host.	[47]
Effects on Gut Microbiota	• ALA have been shown to modulate the gut microbiota without significantly reducing microbial diversity, highlighting their potential role in maintaining gut health.	[48]
Cancer	• ALA acts as a biological antioxidant by scavenging ROS and replenishing endogenous antioxidants, which contributes to its ability to induce cell death in various types of cancer, including breast cancer, lung cancer, and colorectal cancer.	[49]

Antidiabetic as well as diabetic neuropathy potential of ALA

DM is one of the most significant metabolic illnesses, affecting roughly 537 million people globally [17, 18]. Emergent data advocates that DM is caused by increased Reactive Oxygen Species (ROS) making, and diminished antioxidant potential [19]. Various research studies have emphasized the possible therapeutic application of ALA in diabetes due to its capacity to decrease both blood sugar levels in insulin-sensitive and insulin-resistant muscle tissues [20].

Agathos *et al.* [21] conducted a 40-day prospective, interventional study to investigate the efficacy of ALA (600 mg/day, orally given) on 72 diabetic patients with neuropathy who additionally utilized their prescription diabetic drugs. Blood samples were also obtained to determine baseline and second-visit levels. The responses to the survey showed that neuropathy symptoms decreased throughout the two sessions. In laboratory data, average fasting levels of triglycerides were considerably lower, but other indicators were unchanged during the two different visits. The study found that ALA consumption improved the quality of life of diabetic neuropathy patients while also lowering the main warning signs and triglyceride levels.

Antioxidant capabilities of ALA

Numerous studies have been conducted on the antioxidant properties of ALA and DHLA. They act as metal chelating agents and free radical scavengers. They also assist in regenerating naturally occurring antioxidants, including glutathione, vitamins C and E, and repair damage caused by oxidation [5]. ALA therapy caused a reduction in iron ions in the epithelial cells [22]. This decrease was then followed by an increase in the cell's resistance to hydrogen peroxide. This suggests that ALA plays a direct role in reducing oxidative stress. ALA is commonly known as a biological antioxidant that is soluble in both water and fat. It has the ability to neutralize ROS throughout the body, both inside and outside of cells. Therefore, ALA is commonly referred to as the universal antioxidant [23].

Neurologically protective effects of ALA

Free radical-induced damage has a significant impact on subsequent neuronal brain injury after stroke treatment [24]. There is, however, presently no medication accessible to mitigate this impact. The antioxidant property of ALA is associated with its neurorestorative and neuroprotective effects. ALA administration (20 mg/kg) through the jugular vein delivers neuroprotection by plummeting mortality, neurological defect score, infarction, augmented neurogenesis, and brain cell uptake [6]. ALA produces the M2 phenotype in microglia, controls the production of cytokines that promote inflammation (IL-6, IL-1, IL-10, and TNF), and restricts the gene transcription of Nuclear Factor Kappa B (NF-κB), a critical arbiter of responses to inflammation [25, 26].

Oxidative stress is known to cause the degeneration of dopaminergic neurons in Parkinson's disease. Studies have shown that combining ALA and omega-3 fatty acids has an additional effect on reducing cognitive deterioration and improving functioning in Alzheimer's disease [25-27]. Apart from that, ALA has shown potential benefits in treating other neurodegenerative diseases, such as Huntington's disease and ataxia telangiectasia [28].

Cardiac disease prevention effects of ALA

Oxidative alteration of low-density lipoprotein enhances atherogenicity [8]. Elevated oxidative stressors and inflammatory activity produce hydroxyl radicals, peroxides, and superoxides within the tissue called the endothelium, hastening the onset of heart disease. Inflammatory diseases proceed to affect the blood vessels one by one [7]. DHLA has been shown to modulate blood lipids, protect against Low-Density Lipoprotein (LDL) oxidation, and reduce high blood pressure, demonstrating that ALA may be a preventive agent against cardiovascular illness [7].

Role of ALA in Pregnancy

Given ALA's claiming antioxidant properties and influence in a variety of inflammation-related conditions, the latest research has more and more emphasized its role in physiological functions such as pregnancy [29]. The study investigated the effects of ALA vaginal administration in female Wistar rats. Specifically, the researchers examined the tissue distribution of ALA following vaginal administration, its impact on the implementation process (referring to the initial stages of pregnancy where the fertilized egg attaches to the uterine wall), and its efficacy in preventing or inducing preterm birth. Surprisingly, the authors discovered that vaginal ALA is well-absorbed and disseminated despite interfering with the implementation manipulation and they discovered it may even substantially reverse the adverse effects of mifepristone and prostaglandin E2, hindering delivery and lowering the production of mRNA and inflammatory substances production of cytokines [29].

Role of ALA in Protection against renal-related diseases

Hyperglycemia and hypertension are indeed critical risk factors for the development and progression of Chronic Kidney Disease (CKD). High levels of glucose in the blood can lead to damage to the small blood vessels in the kidneys, while hypertension can cause damage to the larger blood vessels and impair kidney function over time [30].

ROS and oxidative stress are also implicated in kidney damage and ischemia-reperfusion injury, which occurs when blood flow is restored to tissues after a period of ischemia (lack of blood supply). This reperfusion phase can exacerbate tissue damage due to the generation of ROS and inflammatory responses [31].

Research suggests that ALA may offer therapeutic benefits for kidney disease. These findings suggest that ALA may have protective effects on the kidneys by mitigating oxidative stress, inflammation, and endothelial dysfunction, which are key factors in the progression of kidney disease [32, 33].

Overall, ALA shows promise as a potential therapeutic intervention for kidney diseases, particularly in conditions like Autosomal Dominant Polycystic Kidney Disease (ADPKD), where metabolic and inflammatory dysregulation play significant roles in disease pathogenesis. Further research is needed to elucidate the mechanisms underlying ALA's effects on kidney function and to determine its optimal dosage and duration of treatment in different kidney disorders [32-34].

Antimicrobial activity of ALA

ALA demonstrates a diverse array of properties, including antimicrobial, antifungal, antinematodal, and antiviral activities, impacting various targets within the body. Regarding its antifungal activity, ALA has been shown to inhibit the growth of *Candida albicans*, a common fungal pathogen, with its effectiveness being directly proportional to its concentration. ALA's ability to penetrate the nucleus and influence intracellular actin-based mobility further underscores its potential as an antifungal agent [34].

Moreover, ALA exhibits promise in protecting against mycotoxins and treating mycotoxicosis, as well as mitigating aflatoxin B1-induced oxidative damage in the liver. These findings highlight ALA's potential in combating fungal infections and their associated toxic effects. This suggests a broader spectrum of biological effects beyond its direct antimicrobial and antifungal properties [26].

In summary, ALA emerges as a multifaceted molecule with significant therapeutic potential against various microbial pathogens, including fungi and nematodes, as well as potentially offering antiviral effects. Further research into the mechanisms underlying these activities could unveil new avenues for the development of ALA-based treatments for infectious diseases [26].

Anti-inflammatory potential of ALA

ALA has also been shown to work as a preventive measure against chemotherapy by inhibiting inflammation that is associated with tumorigenesis [35]. ALA can lower inflammatory indicators in patients with heart disease, as oxidative stress is thought to be the primary cause of many CVDs, including hypertensive and cardiac failure. Oxidative damage rises with age, leading to increased ROS formation or decreased antioxidant protection. Several studies have

also shown that infusing irbesartan and ALA into patients with metabolic syndrome reduces inflammatory mediators while increasing endothelial function, both of which are implicated in the beginning of atherosclerosis [36]. In addition, ALA has been shown to safeguard the hepatic from diseases associated with inflammation.

Anti polycystic ovarian syndrome (PCOS) potential of ALA

The simultaneous administration of ALA (400 mg/day) with myo-inositol (1 mg/d) has been demonstrated to improve the endocrine and metabolic symptoms of PCOS. This treatment has also been shown to have a positive effect on insulin outcomes of an oral glucose tolerance test in 90 obese patients [37]. The combined treatment has been found to improve the menstruation rate of women with PCOS, regardless of their metabolic phenotype. When a higher dose of Myo-inositol is added, a more obvious and insulin-independent benefit is observed [38]. Additionally, ALA (400 mg/day) treatment can increase metabolism inefficiency in all PCOS individuals, especially those at high risk of nonalcoholic fatty liver and hyperglycemia [38]. Finally, combined therapy of D-chiro-inositol and ALA may have significant hormonal benefits for women with PCOS [38].

Role of ALA in treating infertility

Infertility, defined as the inability to conceive despite regular unprotected sexual intercourse for at least a year, affects a significant portion of married couples globally, with men accounting for approximately half of infertility cases [39]. While various medications have been used to address issues related to sperm quality, their effectiveness is often limited [40]. Male infertility can result from anatomical anomalies such as ductal obstructions, varicocele, and ejaculatory problems. Reduced sperm production of unknown etiology is estimated to contribute to a considerable proportion of cases [41, 42]. ALA, a potent antioxidant, plays a role in regulating ROS production. Both ALA and its reduced form, DHLA, can neutralize various oxygen-free radical species in aqueous and lipid phases. Available information suggests that ALA may increase sperm motility and minimize sperm DNA damage, hence enhancing overall sperm quality. This suggests the potential of ALA as a therapeutic agent for infertility. Moreover, smoking has detrimental effects on the genital system, leading to conditions such as Hypoxia Inducible Factor (HIF) dysregulation, increased Tumor Necrosis Factor-alpha (TNF-α) levels, activation of caspase 3, and alterations in the Calcitonin Gene Related Peptide (CGRP) in the uterus [43, 44]. ALA has been shown to mitigate the negative impact of smoking on the female reproductive system, highlighting its potential as a protective agent against environmental factors that contribute to infertility [43]. In conclusion, ALA holds promise as a therapeutic option for addressing infertility, particularly in improving sperm quality. Additionally, its protective effects against the reproductive system damage caused by factors like smoking underscore its potential utility in mitigating environmental influences on fertility. Further research and clinical trials are necessary to fully elucidate ALA's role and establish its efficacy in infertility treatment.

Role of ALA in coronavirus disease (COVID-19) protection

Based on a theory [46], ALA has the ability to regulate the immune system by controlling T-cell activation. ALA provides protection against SARS-CoV-2 by opening ATP-dependent K^+ channels (Na^+, K^+-ATPase) in the human host. This, in turn, increases intracellular pH and inhibits virus entry [47].

Effects of ALA on gut microbiota

The process of fermenting vegetables and meat can lead to the production of ALA, a Short Chain Fatty Acid (SCFA). SCFAs like ALA have been shown to modulate the gut microbiota without significantly reducing microbial diversity, highlighting their potential role in maintaining gut health [48].

Interestingly, the insertion of ALA occurs at an intermediate age (around 26–27 d) and has a notable suppressive effect on the accumulation of Esg+cells in aged (40 d) Drosophila midguts. This suggests that ALA supplementation may have potential benefits in counteracting age-related changes in intestinal stem cell function and gut health [48].

Overall, the findings suggest that ALA, derived from fermentation processes, can play a role in preserving intestinal stem cell function and may have implications for maintaining gut health and longevity. Further research is needed to elucidate the precise mechanisms underlying the effects of ALA on intestinal stem cells and its potential applications in promoting healthy aging.

Alpha-Lipoic Acid (ALA) and cancer

ALA emerges as a promising agent in cancer prevention and treatment, with numerous studies highlighting its antioxidant properties and its role in cellular growth regulation. ALA acts as a biological antioxidant by scavenging ROS and replenishing endogenous antioxidants, which contributes to its ability to induce cell death in various types of cancer, including breast cancer, lung cancer, and colorectal cancer [49].

Research indicates that ALA triggers the mitochondrial apoptotic pathway in cancer cells, leading to programmed cell death. Additionally, ALA has been implicated in cancers related to metabolism, further underscoring its potential therapeutic relevance in targeting cancer cells [49].

Studies have demonstrated that ALA can also induce the production of ROS, which enhances ALA-dependent cellular death, specifically in lung cancer, breast cancer, and colon cancer. This suggests that ALA activates the mitochondrial pathway of apoptosis, leading to the demise of cancer cells [49-51]. Recent investigations have explored the impact of ALA on the movement and spread of breast cancer cells, further highlighting its potential as a therapeutic agent in cancer management [49-51].

In summary, the accumulating body of research suggests that ALA holds promise for both cancer prevention and treatment. Its ability to regulate oxidative stress, induce apoptosis, and interfere with cancer cell metabolism makes it an intriguing candidate for further exploration in the field of oncology. However, additional studies are warranted to elucidate the precise mechanisms of ALA's anticancer effects and to optimize its therapeutic potential in various types of cancer [52-54].

A summary of the therapeutic potential of ALA is available in table 1**.**

Molecular targeting

ALA has been found to exert its effects through the modulation of various signaling pathways and molecular targets [55, 56]. PPAR-γ is a nuclear receptor involved in the regulation of glucose and lipid metabolism, making it a potential target for diabetes management and metabolic disorders [57]. JNK is a member of the Mitogen-Activated Protein Kinase (MAPK) family and is implicated in processes related to tumorigenesis and neurodegenerative disorders [58]. In response to glucose fluctuations, ALA exhibits neuroprotective effects by increasing the expression of TrkA/p75NTR and phosphorylated AKT (p-AKT)/AKT pathways. This suggests a potential role for ALA in mitigating neuronal damage associated with conditions like diabetes or neurodegenerative diseases [59, 60]. Furthermore, ALA influences cellular functions such as T-cell proliferation and function by modulating intracellular cyclic Adenosine Monophosphate (cAMP) levels, leading to alterations in Interleukin-2 (IL-2) and IL-2 Receptor alpha (IL-2Rα or CD25) expression. Additionally, ALA enhances the activity of Natural Killer (NK) cells, which play crucial roles in immune surveillance and antitumor responses [61]. Moreover, ALA exhibits antioxidant properties and activates phase II detoxifying enzymes via Nuclear factor erythroid 2-related factor 2 (Nrf2) signaling, thereby protecting cells from oxidative stress-induced damage. It also enhances endothelial Nitric Oxide Synthase (eNOS) activity and reduces the expression of matrix metalloproteinase-9 (MMP-9) and Vascular Cell Adhesion Molecule-1 (VCAM-1) through repression of NF-κB signaling, suggesting potential cardiovascular protective effects [61]. Additionally, both ALA and its reduced counterpart, dihydrolipoic acid, can act as an oxidant couple to modify protein structure by forming heterogeneous disulfides. Notably, positive

effects of ALA have been observed at relatively low micromolar concentrations, indicating its therapeutic potential beyond mere antioxidant activity [61]. Overall, the diverse molecular targets and pathways influenced by ALA underscore its potential as a therapeutic agent for various diseases and conditions, ranging from metabolic disorders to neurodegenerative diseases and immune modulation. Further research into the precise mechanisms of action of ALA will undoubtedly uncover additional therapeutic avenues and optimize its clinical utility.

Pharmacokinetics and bioavailability of ALA

Whereas ALA has a variety of biological functions, investigations have found that its medicinal usefulness is restricted owing to its pharmacokinetics. Research shows a brief half-life and around 30% bioavailability because of several processes, such as hepatic deterioration, decreased dissolution, and gastrointestinal destabilization [4]. However, this is being greatly enhanced by the introduction of novel formulations that effectively boost ALA bioavailable.

The quantity of ALA in plasma and human cells is insufficient to fulfill biological requirements unless we consume it through food. Dietary consumption of ALA has greatly grown to meet the body's energy requirements. Studies have shown that taking a combination of R and S isomers orally while fasting increases ALA absorption by 40% while consuming it with food reduces it by 20%. The effectiveness of the ALA R isomer is more stable in plasma and better absorbed. ALA may be obtained via food to meet biological needs and from natural sources that are naturally occurring. As mentioned earlier, ALA is found in red meat, kidney, liver, and heart of animals. The vegetable spinach, tomatoes, Brussels sprouts, broccoli, peas from the garden, potatoes, and the bran of rice are also great sources of ALA [14]. When given as a component mixture with γ-cyclodextrins, the R enantiomer of Lipoic Acid (RLA) showed an increased absorption rate via the colon. When taken orally or injected intraduodenally, RLA/γ-Cyclodextrins (CD) showed higher plasma access and greater AUC compared to non-included R-lipoic acid [62]. One research included 18 people from both genders, nine girls and nine men, and pharmacokinetic variables were determined to determine the bioavailability of ALA. To improve the absorption of ALA into cells, the researchers utilized lecithin, an amphiphilic matrix that is weakly dissolving. According to a study, ALA tablets and soft gel capsules with a dose of 600 mg showed similar bioavailability and pharmacokinetic characteristics but were more effective than traditional ALA supplements that are usually insoluble [62]. A prior investigation found that the bioavailability of the R isomer was larger than that of the S isomer for all oral doses, with the bioavailability of the R isomer being highest by oral solution [62]. Administering ALA orally in liquid form increases bioavailability, stability, plasma concentrations, and absorption [62].

Perspectives and directions for the future

Absolutely understanding how ALA interacts with cellular targets and signaling pathways is crucial for maximizing its therapeutic benefits. While ALA has demonstrated diverse pharmacological effects in various studies, including enhancing cognitive function and promoting weight loss in aged rodents through AMPK-dependent mechanisms, the precise molecular pathways through which ALA exerts these effects are still not fully understood. Investigating whether ALA directly influences hormonal signaling pathways is an important area of research that could shed light on its mechanisms of action. Hormones play a central role in regulating numerous physiological processes, and if ALA indeed interacts with hormonal signaling, it could have far-reaching implications for its therapeutic applications. The discovery of AMPK-dependent mechanisms underlying ALA's effects on learning, memory, and appetite regulation in aged rodents highlights the complexity of its actions within the body. Understanding how ALA activates or modulates AMPK signaling could provide valuable insights into its potential use as a therapeutic agent for conditions such as cognitive decline and obesity. Further research into the specific cellular targets and signaling pathways affected by ALA will not only enhance our understanding of its therapeutic potential but also pave the way for the development of more targeted and effective interventions. By unraveling the intricacies of ALA's interactions with the body's molecular machinery, we can harness its full therapeutic power for the benefit of human health.

CONCLUSION

Different preclinical and clinical studies form the foundation of much of the discussion presented here. As a result of this, ALA possesses strong anti-disease characteristics, including those for malignancies, metabolic disorders, PCOS, COVID-19, Parkinson's disease, Alzheimer's disease, Huntington's disease, and telangiectasia ataxia, neuroprotective activity, and inflammatory ailments. Liquid ALA preparations have been experimentally demonstrated to have greater levels of plasma and bioavailability than solid doses. Age influences ALA bioavailability, although sexual orientation seems to have minimal impact. As a result, developing superior preparations which can promote ALA absorption is critical for dramatically increasing its bioavailability and, eventually, its therapeutic effectiveness.

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AUTHORS CONTRIBUTIONS

The author confirms the sole responsibility for the conception of the study, presented results, and manuscript preparation.

CONFLICT OF INTERESTS

Declared none

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