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AN UPDATE REGARDING THE POTENTIAL PHARMACOLOGICAL APPLICATIONS OF ALPHA-LIPOIC ACID

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Abstract

Several disorders have been linked to the onset and progression of oxidative stress. An oxidative imbalance in the cell sets in motion a chain of events that leads to cell death. Antioxidant therapy has been identified as a potential palliative treatment, with benefits including slowed disease progression, reduced cell disintegration, and improved cellular activities. An organosulfur molecule called Alpha-lipoic acid (ALA) is a well-known antioxidant that has been examined in a range of disease models. It's expected to be a potent micronutrient with a diverse set of pharmacological actions. It improves energy metabolism by optimizing the use of glucose and fatty acids. ALA also aids in the reduction of oxidative stress and the counteraction of inflammatory stimuli. A review of the literature was conducted using peer-reviewed journal articles to identify laboratory, animal, and clinical studies that have studied the most recent and advanced innovations regarding the possible pharmacological uses of ALA in the suppression of various pathological biomarkers.

Keywords: Alpha lipoic acid, Anti-inflammatory, Antidiabetic, Antioxidant.

Introduction

Reactive oxygen species (ROS) are important intermediates in the activation of NF-kB [1], which increases the production of proteins that control immunological, inflammatory, and apoptotic processes. Natural bioactive compounds have antioxidant properties. They can act as ROS scavengers [2-4]. Alpha-lipoic acid (ALA), also known as thioctic acid, is a short-chain fatty acid that occurs naturally. The kidney, the heart, and the liver all contain ALA. Spinach, broccoli, and tomatoes are the most abundant plant sources of ALA [5,6]. ALA has been demonstrated to limit NF-kB translocation to the nucleus and activation, resulting in a reduction in cytotoxic cytokine production [7]. Furthermore, ALA and DHLA have been discovered to be highly reactive to a range of ROS [5,8]. ALA and DHLA have been suggested to have anti-inflammatory properties. ALA is a powerful reducing agent that can degrade oxidized versions of a variety of antioxidants, including vitamin C and GSH [9]. ALA's ability to recycle GSH from Glutathione disulfide, as well as its participation in GSH synthesis, contribute to GSH regeneration [10]. In this regard, ALA has been shown to boost nuclear Nrf2 levels, a transcription factor that regulates GSH synthesis [11,7]. Dietary treatment with ALA reduced oxidative stress while restoring the levels of other antioxidants that had been depleted [12,13]. As a medicinal agent and nutritional supplement, the use of ALA as alternative medicine is rapidly increasing [14,15]. ALA's antioxidant and anti-inflammatory properties have been shown to protect against the damage caused by a variety of illnesses, including neurodegenerative disorders [16-18]. This is further supported by the ALA's capacity to traverse the blood-brain barrier [12]. ALA has been shown to improve glucose sensitivity in tissues [19]. Exposure to ALA enhances glucose uptake by translocation of glucose transporters to the plasma membrane, according to studies on muscle cell lines, and further research confirms the function of insulin-mediated PI3K activity in LA-induced glucose uptake [15,10,20]. Because of these qualities, ALA has been studied as a diabetic medication in both experimental animals and humans [21].

Effects of Alpha-lipoic acid in obese children and adolescents.

Obesity is linked to low-grade chronic systemic inflammation. Tumor necrosis factor-alpha (TNF- α), interleukin IL-1, and IL-6 are pro-inflammatory cytokines produced by aggregated adipose tissue [22]. Reactive oxygen species (ROS) are produced mostly by adipose tissue, which is significantly linked to increased oxidative stress [23]. Adipokines cause the generation of reactive oxygen species (ROS), which causes oxidative stress, which causes the synthesis of further adipokines, which increases the production of cytokines, resulting in the development of obesity-related issues [9]. The peroxidation of polyunsaturated fatty acids produces malondialdehyde (MDA). The quantity of oxidative stress is mirrored by the amount of MDA [23]. Multiple studies have demonstrated that ALA can help overweight animals and humans lose weight [24], but there are no statistics in pediatrics. The purpose of this study is to see how ALA impacts overweight children's weight, BMI, leptin, adiponectin, malondialdehyde (MDA), and TNF levels. The researchers evaluated weight, BMI, lipid profile, fasting blood glucose (FBG), malondialdehyde (MDA), and tumor necrosis factor-alpha (TNF- α) levels. The levels of leptin and adiponectin were all tested. When compared to the control group, the ALA treatment group had a significant reduction in weight, BMI, MDA, TNF- α, and leptin levels, but a significant increase in adiponectin levels ($P < 0.05$), but no effect on FBG or lipid profile ($P > 0.05$). For obese adolescents and children, ALA may be administered as a weight-loss supplement [25].

Antioxidant effect of Alpha-lipoic acid in 6-Hydroxydopamine unilateral intrastriatal injected Rats.

Parkinson's disease (PD) is a neurological condition that affects many people. It's linked to Lewy bodies and the substantia nigra's loss of dopamine (DA)-producing neurons. The pathogenesis of PD has been linked to many nervous system locations, neurotransmitters, and protein aggregates [26]. Oxidative stress (OS), inflammation, autophagy, apoptosis, protein aggregation, and changes in

neurotransmitter levels are all caused by a complex interaction between genetic and environmental variables. OS appears to be crucial in the etiology of Parkinson's disease. The inequality between the generation and elimination of reactive oxygen species causes oxidative stress (ROS). The activity of glutathione peroxidases (GPx), which includes eight isoforms involved in H_2O_2 detoxification, is low in dopaminergic neurons in the substantia nigra. The ability of sulfhydryl antioxidants in the striatum to neutralize H_2O_2 in vivo has been linked with their defensive anti-degenerative properties [27]. 6-hydroxydopamine (6-OHDA) is a dopamine (DA) analog that is highly oxidizable. It is a neurotoxin that is commonly utilized to mimic distinct cell progressions seen in Parkinson's disease (PD). It is a useful model for evaluating the features of potentially neuroprotective medicines because its neurotoxic tool is so similar to those of DA. In unilateral intrastriatal (6-OHDA) injected rats, the effect of Alpha-lipoic acid (ALA) on brain oxidative stress (OS) was investigated. Thiobarbituric acid-reactive substances (TBARS) and glutathione peroxidase (GPx) activity were measured in brain homogenates. In the 6-OHDA treated rats, homogenates revealed an increased TBARS content and decreased GPx activity, both of which are suggestive of OS. These variations were reduced by using ALA at the same time. This result supports the idea that a low dose of ALA could help reduce the neurotoxic 6-OHDA's OS [28].

Effects of the combination of Alpha-lipoic acid (ALA) and Coenzyme Q10 (CoQ10) on cisplatin-induced nephrotoxicity

Cisplatin is a platinum anticancer drug used to treat various types of tumors, including head, neck, and lung cancers. Neurotoxicity, ototoxicity, and nephrotoxicity are linked to the administering of high doses of cisplatin [29]. The production of harmful reactive oxygen species (ROS) is a major cause of cisplatin nephrotoxicity [29]. This study aimed to recognize if coenzyme Q10 (CoQ10) and Alpha-lipoic acid (ALA) (alone or in combination) can avert cisplatin-induced nephrotoxicity in animals, so it can be determined whether CoQ10 and ALA could be given at an early stage of therapy for cisplatin-induced nephrotoxicity. CoQ10 hinders the peroxidation of plasma membrane lipids, it is considered as an antioxidant separate from the mitochondrial membrane. CoQ10 can recover other antioxidants such as vitamins E and C, which exclusively affect the proliferation of ROS [30]. ALA and CoQ10 have common shared properties that encourage their synergistic activity. The ability of CoQ10 to react with the reduced form of Alpha-lipoic acid namely dihydro Alpha-lipoic acid (DHLA), facilitates its presence in the reduced form, thus exploiting antioxidant capability in other extra mitochondrial membranes [31]. Both triggers glutathione and other antioxidant enzymatic activity. ALA and CoQ10 impact mitochondrial function as well as reaction to stress transcription factors. The authors relied on the previously mentioned common features in such a combination that might help in the reduction of cisplatin nephrotoxicity. Rats were randomly divided into 5 groups. Tissue antioxidant activity, inflammatory markers (tumor necrosis factor, TNF), and renal function were valued along with histopathological study. Urinary proteins and renal function tests were considerably greater within (cisplatin control group) compared with other groups (*P*-value <0.001). Creatinine clearance was significantly larger with the combination therapy group compared to other groups. Both TNF and malondialdehyde (MDA) were expressively higher within the cisplatin control group while superoxide dismutase (SOD), GSH content, and catalase were significantly lower in the cisplatin control group. When combination therapy was used, MDA level was significantly lower. Histologically, noticeable renal damage was well observed in the cisplatin group, however, the least renal damage was seen in the combination group. This study has well established the role of antioxidants in averting nephrotoxicity caused by cisplatin; the combined therapy with CoQ10 and ALA have a superior prophylactic outcome relative to that of monotherapy [32].

Effect of Alpha-lipoic acid in SARS-CoV-2

The cardiovascular, cerebrovascular, renal, and blood-clotting systems are all affected by SARS-CoV-2. Myocardial infarction, heart failure, myocarditis, arrhythmia, and shock are only a few of the clinical symptoms caused by COVID-19 in the cardiovascular

system. The virus causes direct damage to cardiac cells when it infects them [33]. While inflammatory reactions cause indirect damage, immunological responses and blood coagulation cause hypoxia and ischemia. COVID-19 has been associated with pro-thrombotic diseases, which can lead to thrombosis if clinical symptoms increase [34]. Targeting the reactive oxygen species (ROS) pathway or the repair of the cellular oxidation-reduction equilibrium is one of the more recent therapeutic modules. Increased oxidative stress is linked to severe episodes of viral pneumonia (OS). As a result, it's critical to investigate various tactics for reducing COVID-19's activated OS pathways. ALA can increase nitric oxide (NO) bioavailability by lowering OS and restoring endothelial nitric oxide synthase (eNOS) activity, which leads to improved endothelial function [35]. This could be accomplished by preventing the oxidative degradation of tetrahydrobiopterin (BH4), an important cofactor for eNOS [36,37]. Nuclear factor-kappa B (NF-kB), which is activated by OS, is a target for immune function regulation [38]. One strategy for COVID-19 treatment could be to use antioxidants that block NF-kB signaling. In addition, antioxidant medications protect the host cells from OS caused by the infection. In this context, Alpha-lipoic acid (ALA), a powerful antioxidant, is thought to be an inhibitor of NF-kB activation, boosting the human host's resistance against SARS-CoV-2 [36,39].

Effects of Alpha-lipoic acid on the attenuation of the toxic effects of tissue lipopolysaccharide

Immature pregnancy or abortion can result in infertility in a variety of species. Gram-negative bacteria, such as Escherichia coli, can easily infect the reproductive system and mammary gland, which is thought to be the main source of the above problem. Following the emergence of these illnesses, blood and tissue lipopolysaccharide (LPS) levels significantly increased [40]. The availability of these endotoxins in the follicular fluid can be increased by high amounts of LPS, resulting in an increased incidence of early labor [41]. LPS is a chemical that may reduce the success of in-vitro fertilization-embryo transfer (IVF– ET) by lowering the fertilization rate of mature oocytes, lowering the quality of fertilized oocytes, and lowering the pregnancy rate [42]. LPS increases nuclear factor kappa B (NF-kB) and produces pro-inflammatory cytokines, causing apoptosis and embryo damage before implantation [43]. LPS can potentially damage mitochondria by producing too many reactive oxygen species (ROS) [44]. The quantitative and qualitative parameters of mouse embryos challenged with lipopolysaccharide (LPS) were assessed to show how they respond to alpha-lipoic acid therapy. LPS treatment increased intracellular ROS levels ($P \leq 0.05$) as well as significant reductions ($P \leq 0.05$) in intracellular GSH content, mitochondrial mass, and blastocyst quality. All of the above-mentioned unfavorable effects of LPS were reduced by ALA. In response to LPS, the relative expression levels of Nrf-2 and Tnf-RI/P-60 receptors ($P \leq 0.05$) dramatically increased, while treatment with ALA significantly reduced the relative expression of Tnf-RI/P-60. ALA also improved the developing capacity of LPS-preserved embryos after they had been implanted. As a result, the outcomes of this study suggest that ALA treatment can counteract the toxicity of LPS on reproduction. These qualities were mostly related to advancements in the intracellular antioxidant capacity as well as the defeat of some inflammatory components, such as the TNF-RI/P-60 receptor, which is involved in apoptosis formation. These remarks have important implications for infertility therapy and dairy farming [45].

Effects of Alpha-lipoic acid on the improvement of glucose uptake through DNAJB3 cochaperone

In humans and animal models of obesity with insulin resistance (IR) in type 2 diabetes, the pharmacological impact of ALA in increasing insulin sensitivity and promoting glucose metabolism has been widely explored (T2D). Through its capacity to block JNK and IKK activation, lower IRS1 phosphorylation, and promote the PI3K/AKT pathway, ALA can induce both basal and insulin-mediated translocation of glucose transporters to the plasma membrane. DNAJB3 is a member of the DNAJ/HSP40 cochaperone family with decreased expression in obese[46] and T2D patients[47], and low levels of DNAJB3 have been linked to increased metabolic stress [46]. In 3T3-L1 adipocytes and C2C12 skeletal muscle cells, there is evidence for a

unique role of DNAJB3 in reducing metabolic stress and increasing insulin function, leading to an increase in glucose uptake[47]. ALA could mediate the favorable effects of DNAJB3 depending on the features of DNAJB upregulation in metabolism coupled with ALA administration. As a result, the effect of ALA therapy on DNAJB3 expression in metabolically active cells was studied to determine the implications of this involvement on metabolic stress that triggers IR as well as glucose uptake. In C2C12 and HepG2 cells, ALA can cause a significant rise in DNAJB3 expression. In response to tunicamycin, pre-treatment with ALA significantly reduced the expression of ER stress indicators. The tunicamycin-mediated transcriptional stimulation of ATF6 was significantly reversed by ALA administration, but insulin-stimulated glucose uptake was enhanced. In C2C12 and HepG2 cells, ALA can cause a significant rise in DNAJB3 expression. In response to tunicamycin, pre-treatment with ALA significantly reduced the expression of ER stress indicators. The tunicamycin-mediated transcriptional stimulation of ATF6 was significantly reversed by ALA administration, but insulin-stimulated glucose uptake was enhanced. Surprisingly, silencing DNAJB3 expression canceled ALA's protective function against tunicamycin-induced endoplasmic reticulum (ER) stress, implying that DNAJB3 is a crucial component of ALA-alleviated tunicamycin-induced ER stress. Furthermore, in C2C12 and HepG2 cells transfected with DNAJB3 siRNA, the effect of ALA on insulin-triggered glucose uptake was significantly reduced. All of these findings point to DNAJB3 as a biological mediator by which ALA reduces ER stress and enhances glucose absorption [48].

Protective effect of Alpha-lipoic acid on cisplatin-induced hepatotoxicity in rats

Cisplatin (CIS) is an antineoplastic compound used to treat various types of cancers such as kidney and liver, testis, bladder, ovary, and non-small cell lung cancers. CIS prevents DNA synthesis. CIS produces toxic side effects including hepatotoxicity, nephrotoxicity, cardiotoxicity, and neurotoxicity. Giving CIS in large doses may precipitate liver and kidney toxicity, which restricts CIS therapy. The mechanism of CIS-induced hepatotoxicity is associated with a generation of reactive oxygen species (ROS) [49]. ROS are highly reactive so they deteriorate lipids, proteins, and DNA [50]. ALA is an antioxidant compound that chelates metals, scavenges ROS, and restores cellular antioxidants, such as vitamins C and E, and glutathione [51], which are essential for the endogenous correction of oxidative damage. In this study, the protective properties of ALA on CIS-induced liver damage in rats have been studied. Four equal groups of rats have been used. The control saline solution (0.9%) group; ALA group; CIS group; CIS + ALA group. In the CIS group, Bax, caspase3, malondialdehyde (MDA), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels were elevated, whereas Bcl-2, superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) levels were reduced relative to the control group. In the CIS + ALA group, Bax, caspase 3, MDA, AST, and ALT levels were decreased, whereas Bcl-2, SOD, CAT, and GPx levels were raised in comparison with the CIS group. In the CIS group, it was found an augmented perivenule sinusoid dilation, karyomegaly, pyknotic and karyolytic cells, central vein congestion, parenchymal inflammation, mild bile duct proliferation, and periportal sinusoid dilation. Histological liver deterioration was decreased in the CIS + ALA group. Hopefully, ALA could be implemented in managing CIS-induced liver toxicity due to its powerful antioxidant and anti-inflammatory properties [52].

Effects of Alpha-lipoic acid as an adjuvant for nonsteroidal anti-inflammatory drugs

Alpha-lipoic acid (ALA) has been shown to possess positive effects on gastric ulceration [53]. It could affect oxidative/inflammatory-based diseases, through its strong anti-inflammatory properties in human endothelial cells previously treated with tumor necrosis factor-α through impeding NF-KB translocation in a dose-dependent mode of action. The ulcerogenic negative drawbacks of nonsteroidal anti-inflammatory drugs (NSAIDs) restrict their use. In this study, the synergistic anti-inflammatory properties of combined ALA and Indomethacin (Indo) treatment in mice as well as the anti-inflammatory effect of ALA on the role of Indo in

the induction of gastric damage have been examined. Mice were given 5 or 30 mg/kg Indo (p.o) alone or in combination with ALA given (i.p). Paw thickness and edema in determined to demonstrate the anti-inflammatory effect (In vivo). Gastric mucosal hemorrhage, erosion, edema was assessed to observe gastric inflammation. According to the results, Indo has a sub-therapeutic effect at 5 mg/kg, whereas the co-administration of Indo and ALA has a far greater impact on the reduction of paw edema, suggesting that the anti-inflammatory effects of Indo were boosted by ALA. Indo at 30 mg/kg triggered a significant injury to the stomach prohibited by co-treatment with ALA. Accordingly, combining ALA with NSAIDs can improve anti-inflammatory effects while also preventing NSAID-induced stomach damage. ALA could be a potential adjuvant that reduces the dose required for effective NSAID therapy, improving the safety profile of NSAIDs, especially in cases where long-term high-dose administration is required [54].

Effects of Alpha-lipoic acid on inhibition of lung cancer growth via mTOR-mediated autophagy inhibition

Lung cancer is the greatest cause of cancer-related death, and innovative therapeutics for this disease is still needed. Activation of autophagy is intimately correlated with the progression of cancer [55]. Autophagy is an evolutionary process for destroying defective cellular components. Autophagy is induced to increase cell survival when cells are starved of nutrients and energy and go into apoptosis [56]. In general, cancer cells necessitate greater autophagy participation for adaptive survival than normal cells [56]. Autophagy activation has been shown to mediate the peritumoral monocyte-induced cancer development of human hepatocellular carcinoma, as well as the astrocyte-induced promotion of breast cancer brain metastasis [57]. Inhibition of autophagy has been shown to facilitate the killing of non-small-cell lung cancer cells produced by natural killer cells [55]. As a result, autophagy targeting has been proposed as a possible cancer therapeutic method. Autophagy is a complex biological process [58]. The mammalian target of rapamycin (mTOR) is one of the several regulators involved in autophagy initiation [58]. The effects of Alpha-lipoic acid (ALA), a medication used to treat human diabetes problems, on lung cancer growth were investigated in this study. ALA inhibited lung cancer growth in xenograft mice and decreased lung cancer A549 cell viability, according to the findings. Autophagy activation was reported in human lung malignancies, and ALA inactivated autophagy in A549 cells, according to the findings of this study. ALA also activated the mTOR/p70S6K signaling pathway. ALA-induced inactivation of autophagy was restored and ALA-induced decrease of A549 cell viability was prevented when mTOR was inhibited with rapamycin. Overall, the findings imply that ALA inhibits autophagy via mTOR and hence has therapeutic promise in the treatment of lung cancer [59].

Effects Alpha-lipoic acid on systemic inflammation in type 2 diabetes mellitus patients with prior myocardial infarction

Patients with both coronary artery disease and diabetes mellitus are becoming more common, necessitating a more complete treatment approach. Hyperglycemia, as a pathogenetic basis for diabetes, can cause tissue damage in a variety of ways. When glycolysis is inhibited, other glucose oxidation processes, including polyol and hexosamine, are activated. When the polyol pathway is activated, more reactive oxygen species are produced, resulting in oxidative stress (OS), which is important for initiating smooth muscle cell death and cardiac remodeling [60]. Increased transcription of inflammatory cytokine genes occurs when the hexosamine glucose consumption pathway is activated, contributing to vascular inflammation and proatherogenic conditions. The cytokine system is involved in the pathogenesis of both metabolic illnesses and coronary heart disease, and its activation is a measure of severity and a predictor of disease progression [61]. The beneficial effects of Alpha-lipoic acid (ALA), such as antioxidant capabilities, vasorelaxation, and anti-inflammatory potential [62], are fascinating. Furthermore, the shortage of ALA in diabetes determines the demand for ALA in patients [63]. In the study, patients with type 2 diabetes and a history of non-Q-myocardial infarction were given

oral anti-diabetic medication as well as basic therapy. After four months of treatment with Alpha-lipoic acid, the concentrations of C-Reactive Protein, IL-6, and TNF- were found to be significantly lower in the leading group. According to the findings of this study, consuming Alpha-lipoic acid for four months reduced systemic inflammation activity while not affecting the content of anti-inflammatory IL-10 in individuals with type 2 diabetes who had a non-Q-myocardial infarction. Because of the foregoing, it may be worthwhile to deliver Alpha-lipoic acid to these individuals, given the agent's beneficial properties, which include antioxidant characteristics, vasorelaxation, and anti-inflammatory potential [64].

Effects of Alpha-lipoic acid and resveratrol on mitigation of radiation-induced pneumonitis and Lung Fibrosis

The lungs are an organ that is vulnerable to the harmful effects of ionizing radiation. According to studies, lung exposure to acute and high doses of radiation as a result of inhalation of radioactive substances can cause pneumonitis and fibrosis, both of which are linked to a higher risk of death. Some medications have been explored so far for preventing pneumonitis and fibrosis in mouse lung tissues exposed to ionizing radiation. Several cytokines and chemokines are released after a high dose of radiation given to the lungs, leading to the infiltration of inflammatory cells. Several cytokines are released by macrophages, neutrophils, and lymphocytes, which mediate the formation of edema and pneumonitis. Furthermore, persistent free radical generation, such as reactive oxygen and nitrogen species (ROS and RNS), stimulates collagen deposition in the extracellular space, resulting in fibrosis. Both pneumonitis and fibrosis can kill a person who has been exposed to them. Resveratrol and Alpha-lipoic acid are two powerful antioxidants with proven radioprotective properties. Resveratrol isn't a direct antioxidant, but it can boost the activity of antioxidant enzymes like superoxide dismutase (SOD) and glutathione peroxidase (GPx) in cells [65]. It also stimulates DNA repair and reduces cell mortality in oxidative stress settings by stimulating sirtus-1 (Sirt-1). Treatment with resveratrol before radiation exposure has been shown to reduce radiation toxicity [66]. Alpha-lipoic acid, unlike resveratrol, is a powerful antioxidant that neutralizes free radicals by recycling ascorbic acid and alpha-tocopherol [67]. The goal of this study was to see if Alpha lipoic acid, resveratrol, and their combination had any effect on mice pneumonitis and fibrosis indicators after irradiation. Control, radiation, radiation plus Alpha lipoic acid, radiation plus resveratrol, and radiation plus both resveratrol and Alpha lipoic acid were all given to 25 mice. A cobalt-60 gamma-ray source was used to irradiate the thoracic areas of mice with 18 Gy. The treatments began 24 hours after the irradiation and lasted two weeks. After 100 days, a pathological investigation revealed that radiation exposure caused severe pneumonitis and mild fibrosis. Resveratrol and Alpha lipoic acid, as well as their combination, have been shown to reduce indicators of pneumonitis and fibrosis. Although resveratrol was unable to prevent the infiltration of most inflammatory cells, inflammation, or vascular damage, Alpha-lipoic acid, and its combination were able to prevent the infiltration of most damaged indicators. Following lung irradiation, Alpha-lipoic acid and its combination with resveratrol were able to reduce fibrosis and pneumonitis markers in mice lung tissues. Although resveratrol protects against specific indicators, it is less effective against lung harm. In conclusion, these findings demonstrate that the combination of resveratrol and Alpha-lipoic acid, as compared to the separate forms of these drugs, has a potent mitigating impact [68].

Effects of Alpha-lipoic acid on dry eyes in diabetes

Dry eye disease is a multifactorial chronic condition that affects the ocular surface due to a loss of corneal epithelium integrity and interruption of tear production. Dry eye is frequently linked to environmental variables such as pollution, ozone, UV radiation, and long-term use of preserved eye drops. These variables produce ocular surface inflammation by increasing oxidative stress. An imbalance between the number of reactive oxygen species (ROS) and the activity of protective conjunctival epithelium antioxidant enzymes (SOD, CAT, and GPx) causes ocular surface oxidation. One

of the pathophysiological mechanisms linked with disorders of the ocular surface was an altered balance between matrix metalloproteinases (MMPs) and their inhibitors in tears[69]. The Kelch-like ECH-associated protein 1 (Keap1)-Nrf2-antioxidant response element pathway is important for regulating antioxidant gene expression, maintaining antioxidant status in corneal epithelial cells, and thereby protecting the ocular surface from dry eye illness [70]. As a result, activation of Nfr-2 in corneal epithelial cells can boost antioxidant defenses including SOD, CAT, and GPx [71]. In dry eye models, a recent study found that Nrf-2 activator is beneficial against corneal epithelial cell damage [72]. In tears, ALA can suppress the expression of MMP-2 and MMP-9 while increasing the expression of their tissue inhibitors [73]. ALA may be beneficial in reducing oxidative stress on the ocular surface [74]. ALA enhances lacrimal peroxidase and restores lacrimal production by activating Nrf-2 in ocular surface cells. ALA has been shown to protect rats against radiation-induced lacrimal gland injury, which is achieved by inhibiting activated T cell production and the NF-B signaling pathway, implying a potential therapeutic function for ALA in dry eye illness [75].

Conclusion

The course of many diseases is aided by cellular oxidation. The use of antioxidants has been found to slow the progression of several diseases. The use of ALA as a therapeutic agent and nutritional supplement is fast rising as an alternative treatment. The antioxidant effect of ALA is important in cellular growth because of its ability to scavenge ROS and replenish endogenous antioxidants. In people with related illnesses, consuming ALA lowered inflammatory markers like CRP, IL-6, and TNF-**α**, according to clinical studies. To conclusively demonstrate the therapeutic efficacy of ALA supplementation, more studies with a longer period, a larger sample size, and other ALA formulations are needed.

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