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The Potent Antioxidant Alpha Lipoic Acid

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Abstract

Natural products may be alternative therapies for many diseases. Alpha-lipoic acid is a short-chain fatty acid, which contains sulfur in their structure. It is a potential antioxidant. Both of alpha lipoic acid and its reduced form have been shown to possess anti-oxidant, cardiovascular, cognitive, anti-ageing, detoxifying, anti-inflammatory, anti-cancer, and neuroprotective pharmacological properties. So, this article review aimed to highlight the potential role of alpha lipoic acid as an antioxidant that could be helped with treating many different diseases such as diabetes, peptic ulcer, epileptic, cardiovascular and cystinuria diseases.

Keywords: Diabetes; Alpha-lipoic acid; Cardiovascular disease; Alzheimer's disease

Abbreviations

ALA: Alpha-Lipoic Acid; BMI: Body Mass Index; CAT: Catalase; DM: Diabetes Mellitus; L-MDA: L-Malonaldehyde; STZ: Streptozotocin; TAG: Triacylglycerol; GPx: Glutathione Peroxidase; SOD: Superoxide Dismutase

Introduction

Alpha Lipoic Acid (ALA), is a potent antioxidant, it possesses a wide array of the metabolic benefits including antiobesity, glucose lowering, insulin-sensitizing, and lipid-lowering effects [1]. α-Lipoic Acid (ALA) is a potent antioxidant that exists in our diets, it shows a great capacity when given natural or synthetic drug [2].

ALA is a short-chain fatty acid, which contain sulfur in their structure. There are two forms of ALA, the R form is the main biological active form that is produced by the body while the S form is produced from chemical manufacture and is not biologically active [3]. ALA is reduced to Dihydrolipoic Acid (DHLA). DHLA has a unique characteristic as free radical scavenging and amending oxidative stress and inflammatory pathways [3].

Alpha lipoic acid and DHLA have been shown to possess anti-oxidant, cardiovascular, cognitive, anti-ageing, detoxifying, anti-inflammatory, anti-cancer, and neuroprotective pharmacological properties [4].

Highlights

- Natural products may be alternative therapies for many diseases. They can be consumed in large daily amounts without any side effect.
- Alpha-Lipoic Acid (ALA) is a natural antioxidant compound.
- ALA has been shown to decrease symptoms of the patient suffering from many diseases.

The Chemical Structure of α-Lipoic Acid

Alpha Lipoic Acid (ALA); is also known thioctic acid, which composed of eight-carbon disulfide containing a single chiral center (Figure 1). Four distinct antioxidant actions of LA and DHLA have been observed: Reactive Oxygen species (free radical) scavenging activity, Capacity to regenerate endogenous antioxidant such as glutathione, vitamin C, and vitamin E, metal chelating activity and repair of oxidized proteins [5].

Antioxidant activity

DHLA, the reduced form of ALA, is capable of exerting an antioxidant effect directly by donating electrons to a pro-oxidant or an oxidized molecule. It can regenerate ascorbic acid from dehydroascorbic acid, and it can indirectly regenerate vitamin E back from its oxidized state [6]. As well, ALA metabolites have been shown to have antioxidant effects [7].

ALA, the oxidized form of DHLA, can exert an antioxidant effect. But this does not mean there is any donation of electrons by ALA to a pro-oxidant or oxidized molecule, since there are none to give. However, it has been documented that ALA can inactivate free radicals, which is a significant antioxidant effect [8]. Also, the ability of ALA to chelate metals can produce an antioxidant effect [9]. DHLA can exert a pro-oxidant effect of donating its electrons for the reduction of iron, which can then break down peroxide to the prooxidant hydroxyl radical *via* the Fenton reaction [10]. So, ALA and its reduced form DHLA, can promote antioxidant properties. ALA has been effectively chelate toxic metals directly, and it also indirectly strongly supports the chelation of metals by its ability to increase glutathione levels inside the cells. Glutathione and its associated enzymes play important roles in the ability of the body to chelate and excrete a wide variety of toxins, toxic metals included. Metals known to form complexes directly with ALA and DHLA include manganese, zinc, cadmium, lead, cobalt, nickel, iron, copper, cadmium, arsenic, and mercury.

Free radicals, once formed, are capable of disrupting metabolic activity and cell structure. When this occurs, additional free radicals are produced which, in turn, can result in more extensive damage to cells and tissues. The uncontrolled production of free radicals is thought to be a major contributing factor to many degenerative diseases. Alpha-lipoic acid is unique among biological antioxidants, because it is soluble in both water and lipids. This allows it to

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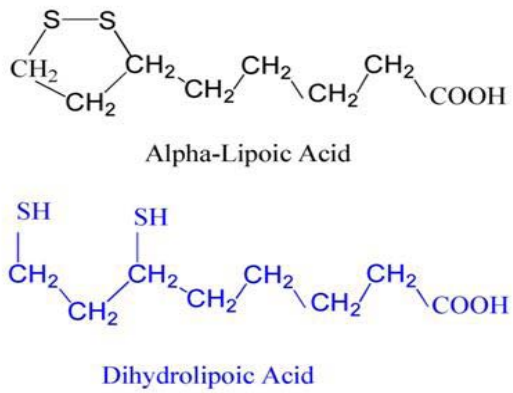

Figure 1: The chemical structure of Alpha lipoic and Dihydrolipoic acid.

neutralize free radicals just about everywhere in the body, inside and outside the cells. Due to its unique sulfur-containing structure, alpha-lipoic acid can scavenge several types of free radicals, such as the highly reactive hydroxyl, and singlet oxygen free radicals. It is also capable of suppressing the generation of free radicals in the first place, since alpha-lipoic acid chelates transition metals, such as iron and copper. Alpha-lipoic acid is involved in many different antioxidant functions in virtually all body tissues, So, it has been called the universal antioxidant [11].

Diabetes mellitus represents a serious global health problem. It is a common disease that's affecting many millions of people all over the world. DM is one of the main effects are the decrease in β-cell mass, which is ubiquitous in most of all patients with type 1 diabetes [12]. Alpha lipoic acid showed a potential role in managing diabetes and improving dyslipidemia and so, it can reduce cardiovascular complications which resulted due to diabetes mellitus. Alpha lipoic acid is able to increase cellular uptake of glucose by recruiting glucose transporter-4 into cell membrane [13]. Alpha lipoic acid has the ability to decrease oxidative stress, which produced by diabetes mellitus by increasing the sensitivity of insulin, thereby maintain glycemic control decrease reactive oxygen species generated by hyperglycemia and dyslipidaemia [14]. In addition, ALA significantly improved deterioration of vitamin C and attenuates the status of antioxidant enzymes and biomarkers of oxidative stress, which arises by diabetes mellitus [14].

α-Lipoic Acid and Obesity

Obesity is an important public health disease that predisposes people to many diseases such diabetes, coronary heart disease, stroke, obstructive-sleep apnea and certain forms of cancer [15].

α-lipoic acid supplementation at a dose of 300 mg/day might help to could help to promote weight loss and fat mass reduction in healthy overweight/obese women following an energy-restricted balanced diet [16]. Moreover, Koh [17] stated that supplementation of α-lipoic acid at a dose of 1200-1800 mg/day together with a low calorie diet, overweight and obese subjects promotes weight loss as well as Body Mass Index (BMI) and waist circumference reduction, but this effect showed only significant at the highest dose.

Carbonelli [18] reported that α-lipoic acid (800 mg/day) promotes the reduction of weight, fat mass and waist circumference in overweight and obese subjects, but not in normal weight subjects, suggesting that these effects could be due to the increased satiety induced by α-lipoic acid. α-lipoic acid could promote weight loss by reducing food intake and stimulating energy expenditure [19].

α-Lipoic Acid and Peptic Ulcer

Peptic ulcer is a gastrointestinal defect, which result due to imbalance between protective and effective agents and it is also due to *H. Pylori* infection. There are several factors as smoking, alcohol, some types of drugs such as aspirin can implicate in ulcer formation [20].

Hcl secretion which can be stimulated by acetylcholine, histamine and stress. Some drugs like Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) cause an inhibition of the bicarbonate production and hence cause the formation of ulcers [21].

Alpha lipoic acid protected the gastric mucosa which covers the stomach wall from damage *via* lowering volume secretion, increment the pH level and mucous secretion [22]. Moreover, Hussein [23] reported that using alpha lipoic acid as a pretreatment of gastric ulcer resulted in an effective protection against ulcer and oxidative damage in gastric mucosa tissue, which induced by ethanol in rats, α-lipoic acid was able to mend serum biochemical parameters such as Nitric Oxide (NO) and Sialic acid, also, GPX, SOD and CAT enzyme as an antioxidant enzymes and non-enzymatic antioxidant as reduced Glutathione (GSH) defense system.

α-Lipoic Acid and Alzheimer's Disease

Alzheimer's Disease (AD) is a neurological disorder that characterized by profound memory loss and progressive dementia. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) have been suggested for the potential treatment of neurodegenerative diseases, such as Alzheimer's Disease (AD). Prolonged use of NSAIDs, however, produces Gastrointestinal (GI) toxicity. The selection of the antioxidant, ALA was based on the proposed role of oxidative stress in the development and/or progression of AD [24]. Alpha lipoic acid has the ability to decrease cognitive impairment and may be a successful therapy for Alzheimer's disease and any disease related dementias. Mitochondria lost its efficiency with age due to the oxidation of proteins, lipids, DNA, and RNA [25].

Alpha lipoic acid increases the production of Acetylcholine (Ach) *via* activating choline acetyl transferase and increases glucose uptake, hence, supplying more acetyl-CoA for the production of Ach of each. Alpha lipoic acid can chelates redox-active transition metals, hence inhibiting the formation of hydroxyl radicals and also scavenges reactive oxygen species, thereby increasing the concentration levels of reduced Glutathione (GSH). Also, a decrease of inflammatory marker is also achieved by the same mechanism. Alpha lipoic acid can scavenge lipid peroxidation products as hydroxynonenal and acrolein. Dihydrolipoic acid, is the active compound which is responsible for the most of these beneficial effects [26,27] (Figure 2).

α-Lipoic Acid and Epileptic

Neuronal cell death may be both a cause and consequence of epileptic seizures. Seizures result in structural rearrangements that could contribute to a life-long state of hyper-excitability [28].

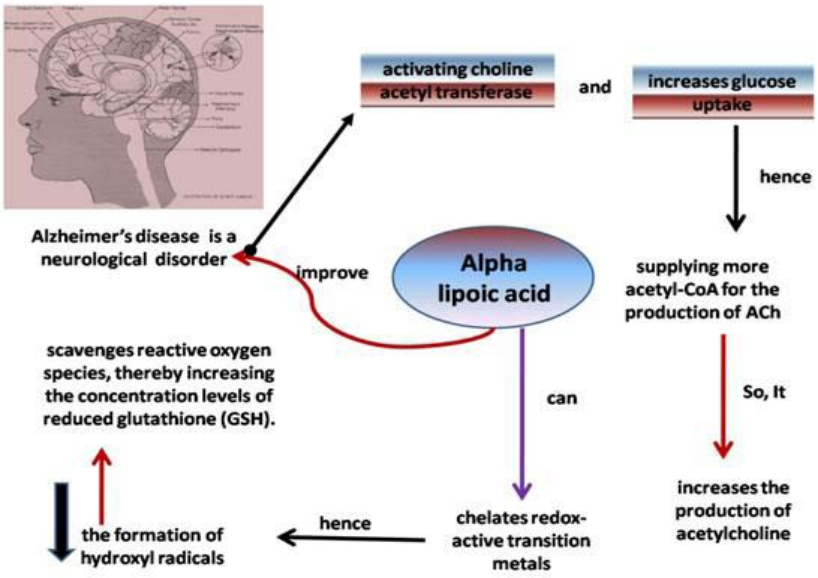

Figure 2: The mechanism action of alpha lipoic acid in controlling Alzheimer's disease.

Alpha-Lipoic Acid (ALA) play a principle role in antioxidant defense in the brain because of their roles as biologic antioxidants. Also, it was previously shown that ALA has neuroprotective effects in experimental brain injury caused by trauma and subarachnoid hemorrhage [29,30].

Lipoic acid pretreatment can treat cognitive dysfunction in pilocarpine-epileptic rats *via* increasing the ChAT and AChE activities in hippocampus [31]. Moreover, Baluchnejadmojarad [32] concluded that ALA pretreatment could block kainic acid, which induced impairment of short term spatial recognition memory in a Y-maze, learning and memory in the passive avoidance test partially through its antioxidant activity.

α-Lipoic Acid and Cardiovascular Disease

Oxidative stress is the primary cause of cardiovascular diseases, which including endothelial dysfunction in atherosclerosis and ischemic heart disease, hypertension, and heart failure. Oxidative stress is increased during aging, which resulted in a significant increase of Reactive Oxygen Species (ROS) or decreased antioxidant defense. Aging is also associated with oxidative stress, which in turn leads to organ dysfunction [33].

ALA act as a defensive agent versus risk factors of cardiovascular disease. ALA may influence the CVD risk *via* the beneficial actions on LDL oxidation, blood lipid profiles, plaque formation and hypertension [34].

ALA has the ability to scavenge ROS, metal chelating, and regenerate, glutathione, vitamins E and C [35]. ALA also has anti-inflammatory properties. ALA can mend vascular function and decrease the atherosclerotic plaque burden. LA is thought to inhibit the Fenton-like-reaction mechanism and inhibit the formation of OH and lipid peroxidation in mitochondria [36].

ALA reacts with ROS, normalizes NADPH oxidase activity, and prevent angiotensin II (Ang II) which induced macrophage, monocyte, and T cell infiltrations. Also, A LA can block Endothelin-1 (AT1) receptors, which improves endothelial function and decrease plaque atherosclerosis [37].

The beneficial effects of ALA are related to scavenged ROS and also NF-kappa B inhibition. It also diminishes the chemokine and adhesion molecules involved in T cell trafficking to repression monocyte-endothelial interactions *via* atherosclerotic plaque. ALA may prevent LDL oxidation *via* decreasing the concentrations of LDL-C, Ox-LDL, serum TAC, and lipoprotein (a) [38]. Moreover, EL Barky [39] stated that ALA has a beneficial effect not only in lowering blood cholesterol levels in STZ-diabetic rats, but also, it can increase the lipid profile levels when their concentrations decreased in response to diabetic complications.

Alpha lipoic acid has a useful effectiveness in forbidding the development of hypertension through decreasing inflammatory cytokine levels in the blood, hence it can prevent the pathological changes in vessel cells and normalizing changes in blood pressure [40].

ALA decreases the activity of hydroxy-methyl-glutaryl-Co-A reductase and increases the activities of lipoprotein lipase and lecithin cholesterol acyl transferase [41]. It also, inhibit the activity of hepatic lipogenic gene expressions and stimulation of TAG-rich lipoprotein clearance and so, blood and liver TAG is normalized [42]. ALA can block acetyl-CoA carboxylase, leading to enhanced mitochondrial fatty acid β-oxidation [43]. ALA, can downregulate the endothelial lipase, which could lead to improvement of HDL-C levels [44].

α-Lipoic Acid and Cystinuria

Cystinuria is a type of kidney stone disease that caused by mutations in the *SLC3A1* and/or *SLC7A9* genes, which permit cystine reabsorption in the renal proximal tubule, and it's characterized by aggressive and recurrent cystine stone formation. It is characterized by defective urinary cystine reabsorption that results in the formation of cystine-based urinary stones [45].

ALA inhibits cystine stone formation *via* promoting cystine transport and metabolism. α-LA treatment has been shown to increase Nrf2 nuclear localization and the transcription of Nrf2-regulated genes that promote glutathione biosynthesis *via* cystine import and cellular cysteine utilization [46]. It also increasing the solubility of the urinary system, *via* the excretion of downstream α-LA metabolites into the urine which achieved without changing the pH of the urine [47].

Conclusion

This article, review has abbreviated the fundamental and potential role of alpha lipoic acid as a potent antioxidant that could be helping to treat different diseases such as diabetes mellitus it can lower blood glucose levels and improves insulin sensitivity in diabetic patients. Moreover, it showed a potential role in promoting the reduction of weight, fat mass and waist circumference in overweight and obese subjects. Also, ALA has a potential role in maintaining peptic acid, epileptic, cardiovascular disease and cystinuria diseases.

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