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Exploring the Clinical Pharmacological Characteristics of Lipoid Acid through a Comprehensive Literature Review

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Abstract: In the realm of modern medicine, the prevention of atherosclerosis has emerged as a vital focus area. Atherosclerosis, a condition characterized by the buildup of plaque in arterial walls, poses significant health risks, including heart attacks and strokes. To combat this widespread health concern, researchers have turned their attention to the use of modern antioxidant agents – potentially a groundbreaking solution. However, despite the importance of this task, scientific research in this direction remains limited, specifically in terms of utilizing combined forms of various antioxidants for angioprotection across different age groups. This article delves into the significance of searching for the optimal drug that hinders atherosclerosis development and explores its clinical mechanisms.

The prevention of atherosclerosis remains an integral part of modern medicine's mission to ensure better cardiovascular health worldwide. While modern antioxidant agents offer significant potential, their combined use for angioprotection across different age groups demands more scientific research. The importance of identifying an optimal drug to combat atherosclerosis cannot be overstated, and in-depth studies on clinical mechanisms will contribute greatly to this endeavor. By prioritizing research in this direction, we can strive towards a future where atherosclerosis is effectively prevented, reducing the burden on individuals and healthcare systems alike.

Keywords: α lipoic acid; atherosclerosis; antioxidant therapy; dihydrolipoic acid, dyslipidemia, hypolipidemic.

Introduction. The use of alpha-lipoic acid is currently being highlighted as a promising approach in the treatment of atherosclerosis due to its wide range of effects, considering the diverse mechanisms that lead to the development of this condition and its complex pathogenesis. However, it is worth noting that there is a limited number of scientific studies conducted in this area, with most of the focus being on the treatment of diabetic polyneuropathy.

Metabolic disorders can significantly increase the production of free radicals in the tissues, leading to an ineffective functioning of the body's natural antioxidant defense system and the development of oxidative stress. This, in turn, results in the impairment of vasodilation dependent on nitric oxide (NO) due to the inhibition of NO-synthase activity by superoxide anion. Consequently, there is an elevation in vascular tone, leading to reduced blood flow and tissue ischemia, while also increasing NO production.

As a result of the increased burden on the body's natural antioxidant system, a deficiency in this system has been observed. Therefore, it is crucial to examine lipoic acid (LA), a natural antioxidant. LA's properties have been extensively studied in various settings, including in vitro, animals, and humans, as evidenced by over 1000 scientific articles in databases such as Pubmed, Medline, Scopus, Embase, and Elibrary.

Regarding the pharmacological properties of thioctic acid (TA) or alpha-lipoic acid, it is recognized as a natural coenzyme of the mitochondrial complex and plays a role in the oxidative decarboxylation of pyruvate and α-ketoglutarate acids. It also regulates cellular aerobic energy production processes. The normal concentration of LA in the human body ranges from 1 to 50 ng/ml, and the daily requirement is 1.5 grams. LA was first discovered by E. Snell in 1937 and documented in 1951 and its structural formula was determined to be 1,2-dithiolan-3-valeric acid [1,3,7].

LA is a potent antioxidant substance, primarily because it contains two SH - groups in its molecular structure. These SH - groups enable LA to engage in the restoration process of natural antioxidants such as ascorbic acid, glutathione, coenzyme Q10, and vitamin E. In this process, iron and copper ions play a crucial role in transforming LA into dihydrolipoic acid. One of the significant benefits of LA is its ability to exist in both oxidized and reduced forms, namely lipophilic (lipoic acid) and hydrophilic (dihydrolipoic acid) [4,8,10].

After entering the body, LA is primarily responsible for its therapeutic effects by converting into dihydrolipoic acid. However, although dihydrolipoic acid has potential medicinal uses, it is not utilized due to its susceptibility to oxidation in external environments. Nevertheless, the lipophilic characteristic of LA allows for easy penetration through biological membranes and the blood-brain barrier.

In experimental studies, lipoic acid was found to alter the composition of lipids by increasing the presence of unsaturated fatty acids. This, in turn, promoted protein synthesis and the accumulation of glycogen in the liver. Furthermore, lipoic acid demonstrated antihyperglycemic and antihypertensive effects, leading to the normalization of mitochondrial anion superoxide production. Existing literature highlights the significant impact of lipoic acid on protein kinase (adenosine monophosphate) [2], a crucial active enzyme responsible for maintaining normal tissue metabolism. When administered, lipoic acid restored the antioxidative potential, accelerated glucose oxidation, promoted phosphorylation, and facilitated glycolysis [11].

Since the 1960s, lipoic acid has been utilized for the treatment of various liver conditions, including acute hepatitis A, chronic hepatitis, fatty degeneration of the liver, liver cirrhosis and fibrosis. Additionally, it has been employed to address toxic injuries caused by metals and mushroom poison, hyperlipidemia, atherosclerotic diseases, and diabetic polyneuropathy [12].

The interest in extensively studying this acid in clinical settings emerged following a research conducted by D. Ziegler in 1995. The study, known as ALADIN (Alpha-Lipoic Acid in Diabetic Neuropathy), was a randomized, double-blind, placebo-controlled, multicenter study that investigated the impact of LA on peripheral and cardiovascular autonomic neuropathy in diabetes patients. This research played a crucial role in revising the dosage of lipoic acid for treating diabetic neuropathy and contributed to its recognition in evidence-based medicine. Notably, the study found that a dosage of 600 mg of LA over a three-week period yielded the most significant results [5].

Building on the success of the ALADIN study, subsequent research has been conducted in various medical disciplines. These include ALADIN II (involving 299 patients), ALADIN III (involving 509 patients), ORPIL (Oral pilot conducted by K.J. Ruhnau in 1999, with 24 patients), NATHAN (Neurological assessment of thioctic acid in diabetic neuropathy), and DECAN (assessing cardiovascular autonomic neuropathy, conducted by D. Ziegler and Gries F.A., with 73 patients). These studies have consistently demonstrated the effectiveness and safety of LA [6,9,12].

In 2008, a significant study was conducted by the Linus Pauling Institute at Oregon State University and the University of Washington in the United States. This research focused on the use of a compound called LA (short for the compound's full name) in the treatment of atherosclerosis and vascular inflammatory diseases. The study yielded fascinating results, indicating that LA reduced the formation of atherosclerotic plaques by an average of 50% [13].

Furthermore, the researchers discovered that patients receiving LA experienced significant reductions in the levels of triglycerides, as well as low and very low density lipoproteins in their blood. This finding suggests that LA has a positive impact on lipid profiles, which are directly linked to the development of atherosclerosis. Additionally, it was noted that 40% of cases reported weight loss as a result of the LA treatment [14].

The promising results of this initial study led to further investigations in 2010 and 2017, which corroborated the effectiveness of LA in both the prevention and treatment of atherosclerosis. These subsequent clinical studies provided further evidence supporting the potential of LA as a valuable therapeutic option.

In conclusion, the research conducted at the Linus Pauling Institute, Oregon State University, and the University of Washington in 2008, as well as subsequent studies in 2010 and 2017, have demonstrated the high efficacy of LA in combating atherosclerosis. These findings have significant implications for the prevention and management of this vascular disease [15].

To date, lipoic acid in the form of ethylenediamine, trometamol, and meglumine salts has been registered and is currently being used. A comparison study between the ethylenediamine and trometamol salts of lipoic acid, conducted in a double-blind, placebo-controlled, cross-over design, found that the trometamol salt was effective in reducing H+ concentration and increasing blood alkalinity. This led to the reversal of ketoacidosis, making trometamol salt a promising independent medicine [16].

Although lipoic acid does not accumulate in tissues, its remarkable efficacy in research is attributed to its predominant oxidation and conjugation processes. As a result, lipoic acid exhibits potent antioxidant properties right from the moment it is consumed. Its unique combination of hydrophobic and hydrophilic qualities enables it to function effectively in both hydrophilic environments like the cytoplasm and blood plasma, as well as in hydrophobic environments like cell membranes and lipoproteins [14].

Lipoic acid has been examined as an antioxidant both in laboratory experiments and in living organisms, but these investigations have only taken place in a hyperglycemic environment [9]. However, none of these experimental projects have succeeded in eliminating the growth of the vascular space in living organisms, where an atherosclerotic environment is created. This means that we have not thoroughly explored the effectiveness of lipoic acid in preventing the spread of the degenerative process [5]. Additionally, the peroxidation of lipids and the oxidative breakdown of unsaturated fatty acids result in the production of hydroperoxides, short-chain aldehydes, ketones, and other oxygen-retaining compounds. This condition is considered a major contributing factor to diseases like atherosclerosis, diabetes, and tumors. Therefore, in this literature review, our aim was to determine how lipoic acid can potentially exert antioxidant effects and influence blood lipid levels in experimental animals with induced atherosclerosis [15].

Deficiency of lipoic acid synthetase was discovered in animals subjected to experimental obesity, resulting in a decline in the production of endogenous lipoic acid. Consequently, this deficiency led to an elevation in the levels of inflammatory markers, including tumor necrosis factor-α and monocyte chemoattractant protein-1. Consequently, there was an increase in peroxide oxidation of lipids and oxidative modification of proteins. However, the inclusion of lipoic acid in the animals' dietary intake facilitated a rapid restoration of antioxidant potential and a temporary reduction in the aforementioned parameters. Furthermore, it was observed that

LA amplified the anti-inflammatory impact of glucocorticosteroids and possessed immunostimulatory properties [12, 16].

In the conducted experiments on animals, the inclusion of alpha-lipoic acid (LA) in their diet as a cytoprotective agent resulted in notable improvements. These included the preservation of the function of cardiac myocytes, a decrease in the size of a heart attack by up to 41.5%, the prevention of apoptosis, and the avoidance of postischemic arrhythmia [2,7].

In other studies, rats fed high-calorie choline-deficient diets experienced a decrease in hemoglobin and erythrocyte levels, as well as an increase in leukocyte count. However, the influence of this diet on the overall count of platelets and erythrocytes was not determined. On the other hand, when alpha-lipoic acid was added to the diet of rats with non-alcoholic fatty liver disease, it had a positive protective effect on various aspects of their hematological status [3,4,11].

Overall, these findings highlight the beneficial effects of LA supplementation in animal studies, as well as its potential to mitigate the negative effects of specific dietary imbalances on hematological parameters [2,3,4,7,11].

Based on scientific literature spanning over 50 years, various mechanisms of action of LA have been examined, leading to the categorization of 6 significant indicators of its effectiveness. These indicators include the neurotropic effect, impact on energy metabolism, cytoprotective effect, influence on the body's reactivity, hepatoprotective effect, and detoxification.

Conclusions. Due to the increasing prevalence of atherosclerosis, the search for an efficacious medication that can effectively prevent its progression is imperative. Given that atherosclerosis affects individuals of different age groups, it is crucial to address this condition among people of varying ages.

While current research has delved into the potential of antioxidant agents in mitigating atherosclerosis, the absence of thorough scientific investigations on combined forms of antioxidants hampers our comprehension of their effectiveness. A meticulous examination of existing literature underscores the significance of discovering an optimal medication in the fight against atherosclerosis. This review not only underscores the importance of averting atherosclerosis but also illuminates the necessity of proactively exploring clinical mechanisms to gain a more profound understanding of the condition. By identifying the gaps in research, it becomes evident that comprehensive scientific studies on the utilization of combined antioxidants for angioprotection are noticeably deficient. Addressing this gap in knowledge emerges as a critical priority for contemporary medicine.

Modern antioxidant agents have shown immense promise in combating atherosclerosis owing to their ability to neutralize harmful free radicals. By reducing oxidative stress and inflammation, antioxidants play a pivotal role in maintaining vascular health. However, further exploration into the combined use of multiple antioxidants for angioprotection is required to unlock their full potential in preventing atherosclerosis.

Understanding the clinical mechanisms underlying atherosclerosis is crucial for developing effective preventative strategies. The use of antioxidant agents presents an opportunity to unravel these intricacies by examining their impact on various biomarkers associated with the development of atherosclerosis. Studying the interactions between antioxidants, arterial health, and aging processes holds promise in formulating targeted interventions.

The studies conducted so far have shed light on the clinical and pharmacological properties of lipoic acid. However, its intricate interactions with other medications have not been thoroughly examined and have attracted significant attention. Consequently, it is crucial to investigate the various compound formations of lipoic acid, assess their efficacy, analyze their pharmacokinetics and dynamics, and consequently, prioritize the development and utilization of these drugs.

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