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Effect Of Alpha Lipoic Acid And Captopril In Induced Atherosclerosis In Rabbits

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ABSTRACT

Study beneficial effect of alpha lipoic acid and Captopril on atherosclerotic rabbits. Atherosclerosis, a leading cause of cardiovascular diseases, is a chronic inflammatory condition characterized by the accumulation of lipids and fibrous elements in the arterial walls. This review evaluates the therapeutic potential of alpha-Alpha lipoic acid (ALA) and captopril, both individually and in combination, in a rabbit model of induced atherosclerosis. ALA, a potent antioxidant, combats oxidative stress and inflammation, while captopril, an angiotensin-converting enzyme (ACE) inhibitor, reduces vascular remodeling and lowers blood pressure. Experimental studies in rabbits with diet-induced atherosclerosis have demonstrated that ALA significantly reduces oxidative stress markers, improves lipid profiles, and enhances endothelial function. Similarly, captopril mitigates vascular inflammation, decreases arterial stiffness, and regulates blood pressure. When co-administered, ALA and captopril exhibit synergistic effects by addressing multiple pathological pathways of atherosclerosis, including oxidative stress, inflammation, and hemodynamic changes.

This review synthesizes current evidence, highlighting the mechanisms through which ALA and captopril confer protective effects against atherosclerosis. Additionally, it explores the impact of this combination therapy on pharmacokinetic parameters, such as Cmax and Tmax, suggesting potential modifications in drug absorption and bioavailability due to co-administration. The findings underscore the therapeutic value of combining antioxidants and ACE inhibitors in managing atherosclerosis and offer insights into their translational potential for clinical applications.

Keywords: *Atherosclerosis, alpha-lipoic acid, captopril, oxidative stress, inflammation.*

1. INTRODUCTION

Atherosclerosis is the major problem of cardiovascular defect that accounts for most of the mortality worldwide **(Zhang *et al.*, 2014; Lopéz *et al.*, 2014**). Newly studies on atherosclerotic plaques revealed that atherosclerosis is a complex pathophysiology where the inflammatory process plays a key role in the onset and progress of the disease **(Libby *et al.*, 2009).** It is well known that increased levels of inflammatory markers are related to elevating rates of cardiac events in patients with coronary artery disease (CAD) **(Hatmi *et al.*, 2010).** Atherosclerosis triggers CAD out of the genesis of a slowly developed lesion, driving to luminal narrowing of the large arteries for the progress of a plaque. Dependent plaque ruptures the most prevalent types of CVD evident such as myocardial infarction (MI), acute coronary syndrome (ACS), and stroke (**Byrne,2016).** Oxidative stress refers to an imbalance between the levels of oxidants and antioxidants, resulting in a disturbance of regulation and potential damage to molecules and cells. Thus, this review is designed to highlight the important roles of oxidative stress on various physiological functions particularly in liver and kidney. Reactive oxygen species (ROS) are highly reactive chemicals generated within cellular mitochondria that can impact plenty physiological functions in either a positive or negative manner. Under normal physiological circumstances, the cells of the body generate a minimal amount of ROS, which corresponds to a low level of oxidative stress. **(Al-Okaily BN ,2024).**

The endothelial lining of arteries regulates tone, hemostasis, and inflammation throughout the circulation. Dysfunction of endothelial cells is an initial step in atherosclerotic lesion formation, particularly in atherosclerosis-prone areas **(Lusis, 2024; Libby, 2002)** Reduced expression of endothelial nitric oxide synthase (eNOS) and superoxide dismutase (SOD) leads to compromised endothelial barrier integrity, increasing the accumulation and retention of low-density lipoproteins (LDL) and remnants of very-low-density lipoproteins (VLDL) and chylomicrons **(Kattoor *et al.*, 2025; Loffredo & Carnevale, 2024)** Endothelial cell activation leads to increased production of reactive oxygen species (ROS), which can cause oxidative modification of apoB-containing lipoproteins **(Akiyama & Ivanov, 2024)**

The abnormal attachment of LDL to intimal proteoglycans is an important step in disease initiation and may explain the atherosclerosis proneness of adaptive intimal thickenings. Oxidation of LDL and cholesterol leads to hyperlipidemia, which plays a role in the formation of atherosclerotic plaques **(Wang & Witztum, 2004).**

Captopril is a first-generation angiotensin-converting enzyme (ACE) inhibitor initially developed in the late 1970s. It was the first orally active ACE inhibitor approved for clinical use and remains a widely used drug due to its efficacy in managing various cardiovascular and renal conditions. Captopril is a sulfhydryl-containing compound, which differentiates it from later ACE inhibitors. Its sulfhydryl group contributes to its potent inhibitory activity on the ACE enzyme and provides antioxidant properties **(Gibbons & Alexander, 2007).** Mechanism of Action: Captopril inhibits the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor, by blocking the ACE enzyme. This results in vasodilation, reduced blood pressure, and decreased workload on the heart. Additionally, captopril reduces aldosterone secretion, decreasing sodium and water retention **(Miller *et al.*, 2015).** Indications: Captopril is indicated for several conditions, including Hypertension. It is effective in lowering blood pressure by relaxing blood vessels. Heart Failure: Improves symptoms and prolongs survival in patients with congestive heart failure **(Zhou *et al.*, 2019).**

Captopril's introduction marked a milestone in cardiovascular medicine, offering a novel mechanism to manage conditions like hypertension and heart failure. Its development paved the way for newer ACE inhibitors with improved pharmacokinetics and fewer side effects. Angiotensinogen converting enzyme inhibitor (ACE inhibitor). can be classified into three groups based on structure sulfhydryl-containing ACE inhibitors related to captopril; dicarboxyl-containing ACE inhibitors related to enalapril (e.g., lisinopril, benazepril, quinapril, moexipril, ramipril, trandolapril, and perindopril); and phosphorus-containing ACE inhibitors related to fosinopril. Many ACE inhibitors are ester-containing prodrugs that are 100–1000 times less potent but have a much better oral bioavailability than the active molecules**. (Marte *et al.*,2022)** Angiotensin II causes blood vessels to constrict and promotes the release of another hormone called aldosterone, which leads to fluid retention. By inhibiting ACE, Captopril helps to relax and widen blood vessels, which 1-reduces blood pressure and improves blood flow **(Smith *and* Vane 2009).** 2- It also decreases the production of aldosterone, 3- reducing fluid retention and reducing the workload on the heart **(Brem *et al.*, 2016).**

2. MECHANISM OF ACTION

The benefits of captopril in hypertension and heart failure result primarily from suppressing the renin-angiotensin-aldosterone system (RAAS). **(Gan *et al.*, 2018)** An angiotensin-converting enzyme (ACE) inhibitor inhibits ACE, converting angiotensin I to angiotensin II. Angiotensin II binds to AT1 receptors on smooth muscles to produce vasoconstriction of precapillary arterioles and postcapillary venules, inhibits the reuptake of norepinephrine (NE), and release of catecholamines from the adrenal medulla, which all increases blood pressure. Angiotensin II also stimulates the adrenal cortex to secrete aldosterone. Aldosterone causes the distal tubules and collecting ducts of the kidneys to reabsorb H_2O and Na^+ in exchange for K, which results in an expansion in extracellular volume and an increase in blood pressure. **(Lezama-Martinez *et al.*, 2018).**

ACE inhibition leads to decreased plasma angiotensin II, leading to vasodilation and decreased aldosterone secretion. Small increases in serum potassium and sodium and fluid loss may occur due to decreased aldosterone secretion. (Chen *et al*., 2018) Administration of captopril results in a reduction of peripheral arterial resistance in hypertensive patients. Regarding the cardiovascular system, ACE inhibitors reduce preload by causing vasodilation and natriuresis, reduce afterload by inhibiting the formation of angiotensin II. The overall effect is the improvement of cardiac output and reduced blood pressure. ACE also metabolizes bradykinin, a peptide that causes vasodilation. ACE inhibitors impede the breakdown of bradykinin, resulting in vasodilation and a bradykinin-evoked cough. The only two ACE inhibitors that do not have to be activated in the body to be effective are lisinopril and captopril while others need to be activated to be effective. **(Herman *et al*.,2023).**

3. PROTECTIVE EFFECT OF CAPTOPRIL ON CARDIOVASCULAR DISEASES

Captopril, an angiotensin-converting enzyme (ACE) inhibitor, has demonstrated significant protective effects against various cardiovascular diseases through multiple mechanisms:

1-Post-Myocardial Infarction (MI) Management:

Captopril has been shown to reduce mortality and morbidity in patients with left ventricular dysfunction following myocardial infarction. The Survival and Ventricular Enlargement (SAVE) trial reported a significant reduction in all-cause mortality and major cardiovascular events in patients treated with captopril compared to placebo**. (Sinha *et al.*, 2015).**

2-Antioxidant Properties:

Captopril exhibits antioxidant effects that contribute to its cardioprotective benefits. Studies have demonstrated its ability to scavenge free radicals, thereby reducing oxidative stress and preventing endothelial dysfunction. For instance, research has shown that captopril can inhibit the oxidation of low-density lipoprotein (LDL), a key factor in the development of atherosclerosis. **(Torzewski, *et al.*,2018)**

3- Anti-Atherosclerotic Effects:

Beyond its antioxidant properties, captopril has been found to attenuate the development of atherosclerotic lesions. In studies involving animal models, captopril significantly inhibited the progression of atherosclerosis without affecting plasma

cholesterol levels, suggesting mechanisms beyond lipid lowering, such as the inhibition of angiotensin II-mediated vascular effects.

4- Radioprotective Effects:

Captopril has demonstrated protective effects against radiation-induced cardiovascular damage. In experimental studies, captopril administration reduced histopathological changes and modulated the expression of inflammatory cytokines in irradiated cardiac tissues, indicating its potential role in mitigating radiation-induced heart damage (Capece *et al.*,2017).

5-Protection Against Ischemic Stress:

Captopril has been shown to protect against ischemic stress by preserving magnesium levels, which are crucial for cardiovascular health.(Al-Ani, and Hasan. 2022.) Magnesium deficiency is associated with increased oxidative stress and susceptibility to ischemic injury. Captopril's antioxidant properties, attributed to its sulfhydryl group, contribute to its protective effects in ischemic conditions.

4. EFFECT OF CAPTOPRIL ON ATHEROSCLEROSIS

Captopril and other ACE inhibitors have been studied not only for their blood pressure-lowering effects but also for potential benefits in the context of atherosclerosis. It is important in managing various cardiovascular conditions, including atherosclerosis. ACE inhibitors like captopril can promote vasodilation, of blood vessels. This may help improve blood flow and reduce the strain on the heart. (Ramachandran et al., 2012). ACE inhibitors may have favorable effects on endothelial function. The endothelium is the inner lining of blood vessels, and its proper function is essential for maintaining vascular health. Dysfunction of the endothelium is associated with atherosclerosis. ACE inhibitors may have anti-inflammatory and antioxidant properties, which could be beneficial in reducing the progression of atherosclerosis. (Tonini *et al.* 2013). ACE inhibitors may contribute to the stability of atherosclerotic plaques. Unstable plaques are more likely to rupture, leading to the formation of blood clots that can block blood vessels and cause serious cardiovascular events, such as heart attacks or strokes. By promoting plaque stability, ACE inhibitors could potentially reduce the risk of these events. As well as, captopril had effects on Lipid Metabolism: ACE inhibitors might have some impact on lipid metabolism, including the regulation of cholesterol levels. Elevated levels of cholesterol in the blood are a key contributor to the development of athero- sclerosis, so any medication that helps manage cholesterol could potentially have benefits in this context. (Smith *et al.*, 2009) Reduced Oxidative Stress Oxidative stress, resulting from an imbalance between free radicals and antioxidants in the body, is implicated in the progression of atherosclerosis. the ACE inhibitors may have antioxidant properties, helping to reduce oxidative stress and potentially slowing down the oxidative damage associated with atherosclerosis. (Smith et al., 2009: Vallerand et al.,2014: Sinha *et al*., 2015; Brem *et al*., 2016).

5. EFFECT OF CAPTOPRIL ON LIPID PROFILE

Captopril, an ACE inhibitor primarily used to treat hypertension and heart failure, has been shown to have secondary effects on lipid metabolism. These effects may contribute to its overall cardiovascular protective properties, particularly in patients with dyslipidemia. and hyperlipidemia

Captopril has been reported to lower total cholesterol levels modestly. This effect is partly attributed to its ability to reduce oxidative stress, which limits cholesterol oxidation, a key step in atherogenesis. Low-Density Lipoprotein Cholesterol (LDL-C

Captopril may reduce LDL-C levels indirectly by improving endothelial function and reducing inflammation. It also inhibits LDL oxidation, which prevents the formation of foam cells and plaque progression. High-Density Lipoprotein Cholesterol (HDL-C)

Captopril may have a neutral or slightly positive effect on HDL-C levels. Improved endothelial function and reduced oxidative stress may contribute to better HDL functionality. Triglycerides Captopril's effect on triglyceride levels appears to be variable, with some studies showing minor reductions, especially in patients with metabolic syndrome. The sulfhydryl group in captopril confers antioxidant properties, reducing lipid peroxidation and oxidative damage. By inhibiting the renin-angiotensin-aldosterone system (RAAS), captopril decreases systemic inflammation, which plays a role in lipid metabolism dysregulation. Captopril enhances nitric oxide availability, promoting vascular health and better lipid handling. Improved insulin sensitivity in some patients using captopril may indirectly influence lipid metabolism, particularly triglycerides.

Alpha-lipoic acid (ALA), also known as 1,2-dithiolane-3-pentanoic acid, 1,2-dithiolane-3-valeric acid or 6,8-thioctic acid has generated considerable clinical interest as a cellular thiol-replenishing and redox-modulating agent (Rahman, et al., 2011) Alpha- lipoic acid (ALA) is a commonly used dietary supplement that exerts anti-oxidant and anti-inflammatory effects in vivo and in vitro. investigated the mechanisms by which ALA may be conferred protection in models of established atherosclerosis (Ying *et al*.,2010).

The observations of ALA as an antioxidant in vitro and in vivo were previously based on hyperglycemic ambience. However, until now, no experimental design has addressed the question as to whether ALA could work in atherosclerotic atmosphere

in vivo thus preventing the proliferation and propagation of this degenerative disease.

Lipid peroxidation, the oxidative deterioration of the polyunsaturated fatty acids (PUFA), leads to the formation of hydroperoxides, short-chain aldehydes, ketones and other oxygenated compounds. (Al-Okaily and. Murad .,2021) This process is considered responsible for the development of various diseases like atherosclerosis diabetes cancer and may be one of the main contributing factors towards aging (Minqin *et al*.,2003).

6. PROTECTIVE EFFECT OF ALPHA -LIPOIC ACID (ALA) ON CARDIOVASCULAR DISEASES

Alpha lipoic acid (ALA) is a specific antioxidant; it can easily quench radicals, has an amphiphilic character, and does not exhibit any serious side effects (GoraA *et al*.,2015). alpha-lipoic acid (ALA)a compound that contains sulfur in the form of two thiol groups acts as a cofactor for several mitochondrial enzymes by catalyzing the α-ketoacid the antioxidant properties of alpha-lipoic acid (ALA) are based on its ability to directly scavenge ROS, its metal chelating activity, and its potential to react with, and regenerate, other antioxidants such as glutathione and vitamins E and C. also demonstrates anti-inflammatory properties. **(Ali and Hasan. 2024).**

An additional advantage of alpha-lipoic acid (ALA)is its solubility both in water and in fat, which allows it to travel to all parts of the body **(Segall *et al*.,2004)** Because of its special properties, it is able to enter certain parts of the cell that most other antioxidants are not able to reach. This compound acts by many mechanisms and can therefore be a very effective antioxidant.

Hence, alpha-lipoic acid (ALA)is used in various diseases concerning age-dependent oxidative stress. It can be particularly effective in cardiovascular diseases, including ischemic heart disease, hypertension, heart failure, and atherosclerosis, where it may slow aging and prolong lifespan.(Rwayyih, and Al-Azawi. 2024).

7. EFFECT OF ALPHA LIPOIC ACID IN ATHEROSCLEROSIS

Many studies have confirmed that alpha-lipoic acid (ALA) can improve vascular function and decrease the atherosclerotic plaque burden (Catapano *et al*., 2000). By chelating redox-active transition metal ions, alpha-lipoic acid (ALA) is thought to inhibit the Fenton-like-reaction mechanism and inhibit the formation of OH^-. As a consequence, lipid peroxidation is inhibited in mitochondria (Sadowska *et al*.,2014) A crucial regulator of vascular homeostasis is the renin angiotensin-aldosterone system (RAAS). A key role in the pathogenesis of atherosclerosis is played by angiotensin II (Ang II). It induces oxidative stress and creates superoxide anions primarily through the activation of NAD(P)H-oxidase in vascular cells and myocytes. In addition, Ang II activates intracellular signaling pathways and upregulates many inflammation factors including chemokines, cytokines, and growth factors, which have been implicated in atherosclerotic plaque development alpha-lipoic acid (ALA) reacts with ROS, such as superoxide anions normalizes NADPH oxidase activity, and can prevent Ang Induced macrophage, monocyte, and T cell infiltrations. It is also thought that alpha-lipoic acid (ALA) can block AT1 receptors, which improves endothelial function and reduces plaque area in atherosclerosis **(Sola *et al*.,2005).**

8. CONCLUSION

The combination of Alpha -lipoic acid (ALA) and captopril is a promising therapeutic strategy for managing atherosclerosis, a major contributor to cardiovascular diseases. ALA, a potent antioxidant, reduces oxidative stress and improves endothelial function, while captopril, an angiotensin-converting enzyme inhibitor, lowers blood pressure and promotes vasodilation, reducing vascular inflammation and supporting cardiovascular health. When used together, these agents may exhibit synergistic effects, potentially improving outcomes and reducing the risk of major cardiovascular events. Future clinical studies are needed to explore the combination's efficacy and safety.

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