International Journal of Research and Review
Vol. 9; Issue: 1; January 2022
Website: www.ijrrjournal.com
Review Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Antioxidative Potential of *Terminalia catappa* L. Leaves in Reducing Plasma Ox-Ldl in Atherosclerosis

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DOI: https://doi.org/10.52403/ijrr.20220186

ABSTRACT

Atherosclerosis is an illness due to plaque build-up in the artery. The plaque, mainly consisted of fat, cholesterol, calcium would harden and narrows the blood vessels, interfering with the blood distribution. Hypercholesterolemia is one of the main causes of atherosclerosis. Arterial endothelial permeability alterations due to increasing plasma cholesterol levels allow LDL-C to migrate into the artery, resulting in a series of vascular changes. Several complications of atherosclerosis include cardiac arrest, stroke, even death. Due to its fatality and lack of symptoms, it is crucial to prevent atherosclerosis. Terminalia catappa L. has been recognized for its antioxidative properties. It contains flavonoids, especially quercetin that exhibited protective effects in the cardiovascular system as well as hinders cellular damage. Various studies had found that quercetin possess several atheroprotective qualities, reducing inflammation and cell damage caused by ox-LDL, lipid precipitation, atherosclerotic plaque, as well as serum levels of ox-LDL, LDL-C, IL-6, and. TNF-.

Keywords: atherosclerosis, Terminalia catappa L. leaves, ox-LDL, antioxidant, CVD

INTRODUCTION

Despite worldwide advances in the provision of effective and reliable preventative measures, the major cause of mortality and early mortality is still cardiovascular disease (CVD).[1] Asia was responsible for 58% of the 18.6 million CVD mortality globally in 2019.[2] As the continent with the most people and the widest mix of ethnicity, cultures, socioeconomic levels, and health-care systems, Asia presents substantial challenges in CVD prevention and treatment.[3]

Atherosclerosis is a chronic illness that can lead to myocardial infarction, stroke, and cardiovascular disease, among other major problems. Inflammation and changes in lipid metabolism are important in atherogenesis, although the exact linkages and causality of these fundamental processes are unknown. For decades, oxidation of LDL was thought to be the primary atherogenic alteration of LDL within the arterial wall.[4]

Recent studies on the other hand, have accumulated a substantial body of evidence in support of the multiple LDL modification idea.[4] It suggests that inside the blood flow and vascular wall, LDL particles undergo various alterations that alter their size, density, and chemical characteristics. The final stage of this cascade, which results in atherogenic characteristics, is oxidation. Furthermore, new research suggests that oxidized LDL (ox-LDL) has both anti-inflammatory and pro-inflammatory characteristics. Through the activation of macrophages and other cells, ox-LDL can cause inflammation. After all, ox-LDL remains an intriguing target for future research that could shed

light on previously undiscovered aspects of the atherogenic process.

The tropical almond tree (Terminalia catappa L.) is a huge tree found throughout the tropical areas, particularly in coastal locations. T. catappa is a member of the Combretaceae family (Combretum family).[5] Indian almond, Malabar Almond, and Tropical Almond are some of its other names. Beta-kaempferol, terflavin, gentisic acid, and quercetin are among the phytoconstituents found in the plant, particularly in the leaves. Antimicrobial, hepatoprotective, and anti-diabetic properties are found in the leaves.[6,7]

Quercetin is one of the phenolic compounds present in catappa leaves. In recent years, the impact of quercetin has attracted much interest. Through altering vascular flexibility, total blood volume, peripheral vascular pressure, antioxidative, and anti-inflammatory capacities, quercetin helps regulate blood pressure and promote cardiovascular health, according to a substantial body of research. [8] By decreasing ox-LDL-induced lipid buildup in macrophages, altering lipid metabolism, boosting macrophage cholesterol transfer, and preventing foam cell generation, quercetin has been demonstrated to protect against atherosclerosis.[9]

The authors plan to investigate and analyze the antioxidative potential of Terminalia catappa L. leaves in lowering plasma ox-LDL in atherosclerosis, as no previous literature review have addressed the topic.

MATERIALS AND METHODS

A literature review was utilized as the review approach. The literature references are from reputable search engines such as PubMed and ResearchGate, and they are from relevant journals. These search engines look for terms like "atherosclerosis," "ox-LDL," "Terminalia catappa L.", and "quercetin". Quercetin from Terminalia catappa L. leaves utilized for atherosclerosis through ox-LDL modification, were included in the study. Preferred studies should be at least ten years old since their publication date, and no newer studies should contradict the information presented. From the 61 journals examined, 32 were found to be appropriate for use as references in this study. The information is interpreted and assembled into a single scientific literature review after it has been verified and scrutinized for validity, objectivity, and credibility.

RESULTS AND DISCUSSIONS

Atherosclerosis

Atherosclerosis is a condition that develops when plaque accumulates in an artery. This plaque is made up of, calcium, fat, cholesterol, and other chemicals found in the blood that solidify over time and constrict blood arteries. Blood flow is reduced due to the constriction of blood arteries, which affects the distribution of oxygen-rich blood to the organs. Atherosclerosis can lead to significant problems like heart attacks, strokes, and even death. Although the specific etiology of atherosclerosis is unknown, various risk factors exist, including a lack of physical activity, smoking, and a poor diet. [10]

Atherosclerosis often is asymptomatic, therefore causing patients to receive a diagnosis after a heart attack or stroke. Treatments of atherosclerosis include lifestyle change, consumption of medicine, and medical intervention if needed.[10]

Pathophysiology of atherosclerosis

Atherosclerosis plaque forms from the increased plasma cholesterol levels that affect the permeability of endothelial cells, therefore enabling lipids, especially particles of LDL-C, to migrate into the arterial wall. Flowing monocytes then bind to endothelial cells that exhibit integrins such as selectins and VCAM-1, and then by diapedesis, migrates over the subendothelial gap.[11]

Monocytes take on macrophage properties and transform into foamy macrophages once they reach the

subendothelial region. In the subendothelial area, LDL particles oxidize and become powerful chemo attractants. Such mechanisms merely encourage macrophages to generate scavenger receptors (B1, A, CD68, CD36, ox-LDL, and for phosphatidylserine) that bind native and anionic phospholipids as well as modified lipoproteins, resulting in the formation of large intracellular cholesterol. The end result is a set of vascular alterations.[11]

Atherosclerosis Treatment

Atherosclerosis treatments focused on controlling hypertension and hyperlipidemia as well as maintaining hemostasis to prevent thrombotic complications. The first-line therapy for atherosclerosis is statins, an HMG-CoA reductase inhibitor.[12]

Statin, such as atorvastatin and rosuvastatin maintains atherosclerosis by reducing LDL cholesterol levels.[13] Statin contains anti-inflammatory properties that repairs endothelial function and reduce lipid plaques and thrombogenicity, which stabilize and hinder atherosclerotic plaque growth.[14]

High-intensity statin therapy is suggested for ASCVD patients aged 75 and younger. A daily dose of 20 mg rosuvastatin or 80 mg atorvastatin is advised for high-intensity statin therapy. For patients over 75 years old with a medication interaction that raises concerns about statin safety or a history of statin intolerance, moderate-intensity statin therapy is indicated, with daily dosages of 10 mg atorvastatin or rosuvastatin.[15]

High-risked patients with statin intolerance or uncontrollable LDL-C levels with statin therapy should consider cholesterol inhibitor drugs such as ezetimibe.[16]

Common Properties of Terminalia catapa L. Leaves as Therapeutic Modalities

Catappa (Terminalia catappa L.) leaves is a tropical plant in Combretacease family, which grows mainly in tropical areas such as Asia, Africa, and Australia.[17] It has shiny dark green colored leaves, with light green coloring underneath. Generally, it is about 15-25 cm in length and 10-14 cm wide. It is usually obovate shaped with a rounded tip and narrowly subcordate base. The leaves are pinnate, with wavy edges and alternate, with one leaf at every knuckle. When it sheds, the leaves coloring changes to red, yellow, or purple.[18]

Catappa leaves contain several compounds that functions as an antioxidant. Based on phytochemical testing, catappa leaves contains flavonoids such as kaempferol or quercetin, saponin, tritepen, diterpen, fenolik, and tanin that could hinder cellular damage.[19]

Common Properties of Quercetin as Terminalia catappa L. Leaves Therapeutic Modalities

Quercetin is a flavonoid with protective effects in the cardiovascular system, anti-atherosclerosis, anti-inflammation,[20] antioxidant, increasing coronary blood circulation, and reducing capillary fragility.[21] Quercetin are found in several plants, such as catappa leaves.[22]

Several studies had proved that quercetin are effective in hindering cellular senescence, reducing cell damage caused by ox-LDL, and lipid precipitation.[23] Another study found that quercetin possesses an anti-atherosclerotic effect through vascular cell molecule 1 adhesion inhibition and CD80 expression inhibition in human umbilical endothelial vein cell model exposed with oxidative stress induced by peroxide.[24]

Several studies have shown atheroprotective qualities of quercetin in test animals. Quercetin reduces inflammation in rabbits through reducing endothelial adhesion molecules caused by oxLDL and hindering TLR-NF-κB signaling pathway.[25] Another study proposes that the atheroprotective mechanisms of quercetin is associated with increased autophagy and hindering aging.[26] Other studies proves that quercetin significantly reduces atherosclerotic plaques, lipid accumulation,

FC levels as well as increases collagen fibers in atherosclerotic plaques in apoE-/- mice with high fat diet. The protective effects of quercetin against atherosclerosis is achieved through regulating the expression of PPARγ, PCSK9, CD36, ABCA1, and LXRα.[27]

Clinical Effect of Quercetin in Lowering ox-LDL in Atherosclerosis

Due to the general composition and features of the particles, quercetin is advantageous to the blood flow, circulatory system, and vessels.[28] Jia et al. reported that quercetin treatment suppressed fatty deposition in the aorta and atherosclerotic plaque volume, as well as serum levels of, ox-LDL, LDL-C, IL-6 and TNF- in ApoE-/- mice.[27]

Quercetin reduced ROS production and activated the PI3K/AKT signaling pathway in C57BL/6 mice, preventing the formation of atherosclerotic plaques.[29] Furthermore, Cao et al. discovered that giving ApoE-/- mice quercetin relieved substantial atherosclerotic disease, increased autophagosomes, and lowered TNF-, IL-1, and IL-18 levels.[26]

Jiang et al. published a study in 2020 that confirmed quercetin's anti-atherosclerosis capabilities once more. In the mentioned study, throughout 8 weeks, a 20 milligrams per kilogram per day quercetin injection substantially reduced fatty buildup in arterial wall underlying atherosclerotic plaques. Regional and circulatory adhesion molecules, as well as inflammatory stimuli, influence vascular aging and atherosclerosis. According to the findings, quercetin increases Sirt1 density while decreasing serum IL-6 and sIcam-1 levels, as well as VCAM-1 in ApoE/- mice's aorta.[9]

One of the senescent cell's indications is increased -galactosidase activity. In this study, quercetin decreased senescence-associated -galactosidase transcription and improved the cell shape of HAECs. Whilst lowering ROS production, quercetin also inhibited cellular apoptosis and raised mitochondrial membrane capability in a dose-dependent sense. The anti-ox-LDL actions of quercetin have been linked to ECM-receptor interaction, nitrogen metabolism, p53, mTOR overexpression and complement and coagulation cascades. As a result, both in vivo and in vitro, quercetin was observed to diminish atherosclerotic plaques. [9]

To test quercetin's anti-inflammatory capabilities, a study conducted by Xue et al. pretreated RAW264.7 cells with quercetin before stimulating them with ox-LDL. Prior to treatment with ox-LDL at a concentration of 50 g/ml, RAW264.7 cells in 6 well plates were pre-incubated for 24 hours with 20 M quercetin. After the cells were collected, the mRNA levels of IL-1 (Figure 1A) and LOX-1 (Figure 1B) were measured by qRT-PCR.[30]

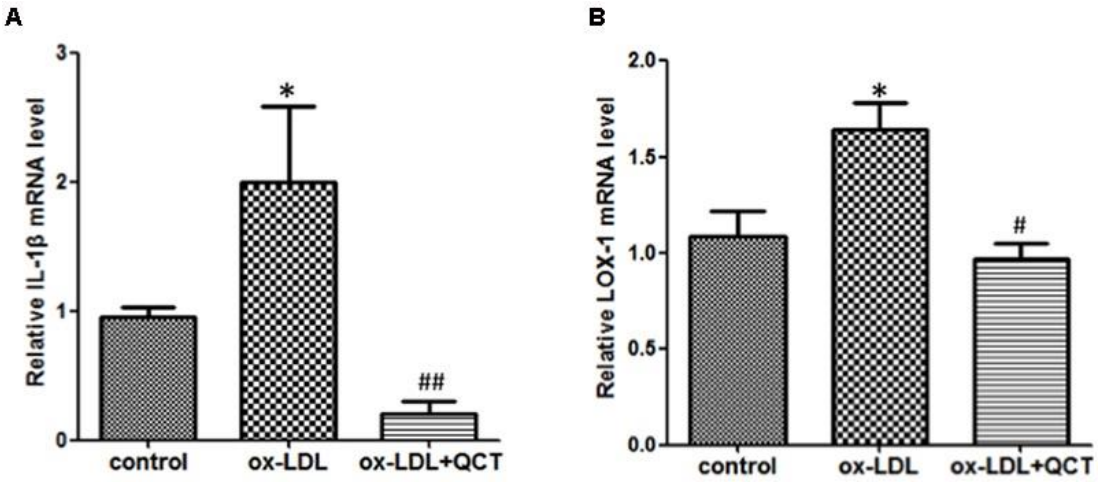

Figure 1. In RAW264.7 cells, quercetin reduced inflammation caused by ox-LDL

In comparison to the control group, ox-LDL activation elevated the mRNA level of the proinflammatory gene IL-1 (Figure 1A) and enhanced the transcription of LOX-1 (Figure B), the ox-LDL receptor. Quercetin therapy inhibited the gene expression of IL-1 (Figure 1A) and LOX-1 (Figure 1B) produced by ox-LDL. The researchers discovered that various amounts of quercetin altered the expression of IL-1 and LOX-1 in response to ox-LDL. Researchers discovered that quercetin decreased the production of the IL-1 and LOX-1 genes in a dose-dependent way. [30]

Terminalia catappa L. Leaves Toxicity Effect

In an acute study, rats given a dose of 2000mg/kg BW Terminalia catappa L. aqueous extract showed no toxicity or death. Toxicity onset and signs of toxicity are also not present. At the end of the chronic toxicity research, there were hardly any notable procedure alterations in hematological, renal, and hepatic parameters such as SGPT, SGOT, glucose cholesterol, urea, uric acid, creatinine, protein, as well as serum ALP activity. It implies that the aqueous extract of Terminalia catappa L. is not harmful in any form. When compared to the dosage of Terminalia catappa L. used in folk medicine, the aqueous extract of Terminalia catappa L. leaves has a wide margin of safety for its beneficial application.[31]

Therapeutic Effect of Terminalia catappa L. Leaves on Atherosclerosis

Catappa leaves could be utilized as a natural and phytotherapy in the treatment of disorders caused by oxidative stress such as atherosclerosis. According to the findings of a study conducted in Nigeria, 80% methanolic leaf extracts from the almond plant had better antioxidant activity than 95% ethanol and water extracts. The findings also suggested that the phenols in almond leaf could have a role in the observed scavenging action. The findings of this study back up recent epidemiological studies that show that consuming catappa leaves can reduce the of chronic diseases linked to oxidative stress and promote overall health benefits due to their antioxidant activity.[32]

CONCLUSION

Quercetin found in Terminalia catappa L. leaves contains immense potential to be utilized as a therapy for atherosclerosis. Various literatures had demonstrated atheroprotective qualities of quercetin in modulating lipid metabolism, inhibiting foam cells production, reducing inflammation and cell damage caused by ox-LDL, lipid precipitation, atherosclerotic plaque, as well as serum levels of ox-LDL, LDL-C, IL-6, and TNF-. Further research and testing are required to continue developing quercetin found in Terminalia catappa L. leaves as a candidate for atherosclerosis prevention.

Acknowledgement: None

Conflict of Interest: None

Source of Funding: None

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How to cite this article: Georgina Mayer Tiberias, Jennifer Jesslina Gunawan. Antioxidative potential of terminalia catappa l. leaves in reducing plasma Ox-Ldl in atherosclerosis. *International Journal of Research and Review*. 2022; 9(1): 745-751. DOI: *https://doi.org/10.52403/ijrr.20220186*

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