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The Potential Therapeutic Role of Bromelin in Pineapple Fruit for Cholesterol: A Comprehensive Literature Review

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ABSTRACT

Background: A main risk factor for cardiovascular illnesses is high cholesterol, which causes 3.6 million deaths yearly by WHO, 2022. Reducing the risk of heart attacks and strokes depends on lowering cholesterol. Recent research indicates that pineapple's bromelain enzyme might help reduce cholesterol levels. This review examines bromelain's potential application in cholesterol management and its effect on cholesterol metabolism.

Objectives: This literature review aims to explore bromelin in pineapple fruit for cholesterol.

Methods: We searched Pubmed, Google Scholar, Scopus, and Web of Science using keywords like cholesterol, lipid metabolism, bromelin and pineapple. We included accessible articles in Bahasa Indonesia or English, including research articles, systematic reviews, meta-analyses, and literature reviews.

Discussion: Bromelain found in pineapple fruit can decrease cholesterol and triglyceride production due to its effects on lipid metabolism, heart function, and anti-inflammatory effects. This is due to their ability to inhibit HMG-CoA reductase production, an important enzyme involved in the liver's cholesterol synthesis.

Conclusion: Bromelin has significant therapeutic potential for reducing cholesterol, especially as a natural supplement to resist lipid-lowering treatments for people who cannot tolerate statins. We need to conduct further research to determine the clinical effectiveness of combination therapy.

KEYWORDS: Cholesterol, Lipid Metabolism, Bromelin, Pineapple

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I. INTRODUCTION

Cholesterol is an essential lipid molecule in various critical biological processes, including cell membrane structure, steroid hormone production, and bile acid synthesis. The liver synthesizes cholesterol endogenously, whereas dietary sources, mainly animal-based foods, obtain it exogenously. The body's balance of cholesterol is critical for maintaining health, as an imbalance can lead to conditions such as atherosclerosis, a significant risk factor for cardiovascular diseases. [1]

This process is significant because increased low-density lipoprotein cholesterol (LDL-C) levels contribute to plaque formation. Cholesterol is essential for cellular function, but an imbalance of very high LDL-C and low high-density lipoprotein cholesterol (HDL-C) increases cardiovascular risk. LDL-C increases arterial plaque, while HDL-C helps remove cholesterol from the arteries. However, hypercholesterolemia remains a public health challenge, requiring ongoing research and interventions to improve cardiovascular outcomes. Cholesterol significantly influences atherosclerosis, defined as the accumulation of fatty deposits in the arterial walls and a major risk factor for heart attacks and strokes. Clinical trials consistently demonstrate that lowering LDL-C significantly reduces the incidence of major cardiovascular events. Decreases in LDL-C significantly reduce the incidence of cardiovascular events, as several clinical studies have demonstrated. High-density lipoprotein cholesterol (HDL-C) is protective by transporting cholesterol from the arteries to the liver for excretion. Therefore, maintaining a healthy balance between LDL-C and HDL-C is very important. [2-3]

The pineapple plant, *ananas comosus*, is the primary source of bromelin, a group of enzymes that break down proteins and have numerous medical uses. 2 Pineapple is a rich source of dietary fiber, vitamins C and B6, manganese, and bromelin—a proteolytic enzyme with anti-inflammatory properties. The fiber content in pineapple can help reduce blood cholesterol levels by binding to cholesterol in the digestive system and facilitating its excretion. Additionally, the antioxidants in pineapple, such as vitamin C, can prevent the oxidative modification of low-density lipoprotein cholesterol, a critical step in the development of atherosclerosis. [4]

This literature review aims to critically assess the role of bromelin in regulating cholesterol levels. In order to provide a thorough evaluation of bromelin's potential in cholesterol treatment, the literature review will address the clinical implications and recommend topics for further investigation.

II. METHODOLOGY

We conducted searches on PubMed, Google Scholar, Scopus, and Web of Science using keywords such as "cholesterol," "lipid metabolism," "bromelin," and "pineapple." Our inclusion criteria encompassed articles in Bahasa Indonesia or English, spanning literature reviews, meta-analyses, systematic reviews, and research articles.

III. LIPID METABOLISM

Lipoproteins are essential for transporting lipids, including cholesterol and triglycerides, through the bloodstream. hey are complicated particles made up of a core of lipids that don't like water and a shell of apolipoproteins, cholesterol, and phospholipids that do. Chylomicrons, very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL) are the main lipoprotein types involved in lipid transport. [5-7]

– *Chylomicrons*

Chylomicrons are the predominant and least dense lipoproteins, which have an essential role in carrying dietary triglycerides and cholesterol from the intestines to peripheral tissues. After lipid absorption in the intestines, chylomicrons enter the lymphatic system and the bloodstream. Lipoprotein lipase (LPL), which is found on the capillary endothelium of fat tissue and muscle, breaks down the triglycerides in chylomicrons into free fatty acids that can be used for energy or stored. The liver absorbs the remaining chylomicrons, which contain high levels of cholesterol.

– *Very low-density lipoproteins (VLDL)*

The liver synthesizes VLDL to transport endogenously produced triglycerides and cholesterol to peripheral tissues. LPL hydrolyzes VLDL particles, similar to chylomicrons, releasing free fatty acids and transforming VLDL into intermediate-density lipoproteins (IDL) and eventually LDL. This process decreases the triglyceride content and increases the cholesterol content of the particles.

– *Low-density lipoproteins (LDL)*

are the primary carriers of cholesterol in peripheral tissues. Cells take up cholesterol-rich LDL particles through receptor-mediated endocytosis. This uptake is crucial for maintaining cellular membrane integrity and steroid hormone synthesis. Elevated

levels of LDL are associated with an increased risk of atherosclerosis, as LDL can infiltrate the arterial wall, become oxidized, and trigger inflammatory processes leading to plaque formation.

– *High-density lipoproteins (HDL)*

are involved in reverse cholesterol transport, a protective mechanism against atherosclerosis. The liver and intestines synthesize HDL particles, which then acquire cholesterol from peripheral tissues and macrophages. The enzyme lecithin-cholesterol acyltransferase (LCAT) esterifies the cholesterol before returning it to the liver for excretion in the bile. HDL also has anti-inflammatory and antioxidant properties, contributing to its protective ragainst cardiovascular disease.

The exogenous and endogenous pathways are crucial for lipid transport in the body, ensuring the distribution and utilization of lipids such as cholesterol and triglycerides. The exogenous pathway involves dietary lipids absorbed in the intestines, packaged into chylomicrons, and transported via the lymphatic system to the bloodstream. Lipoprotein lipase (LPL) then hydrolyzes these triglycerides in peripheral tissues, and the liver takes up the resulting chylomicron remnants. On the other hand, the liver synthesizes lipids through the endogenous pathway, where LPL removes triglycerides and converts very-low-density lipoproteins (VLDL) into low-density lipoproteins (LDL). LDL delivers cholesterol to peripheral tissues, while high-density lipoproteins (HDL) facilitate reverse cholesterol transport back to the liver for excretion. Dysfunction of these pathways can lead to atherosclerosis and cardiovascular diseases, underscoring the importance of lipid homeostasis. [2,7-8]

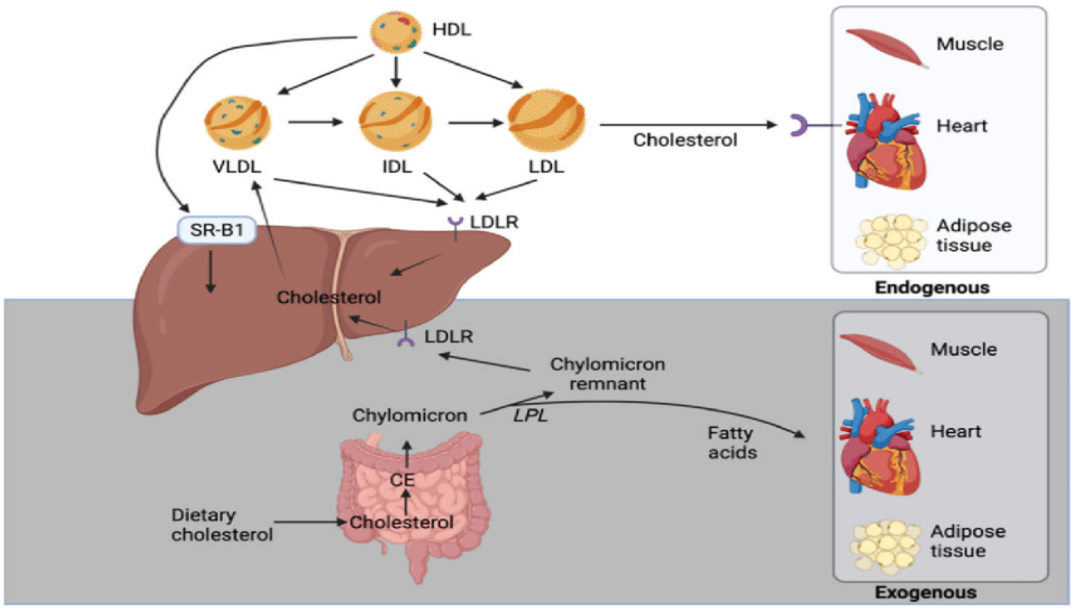

Figure 1. Lipid metabolism

IV. BROMELIN: SOURCES AND MECHANISMS OF ACTION

A. SOURCES

Bromelin is predominantly sourced from the pineapple plant, with the highest concentrations in the stem and fruit. Commercial extraction of bromelin occurs from both these parts, with the stem being the most commonly used due to its higher enzyme content. The extraction process involves crushing the pineapple stem or fruit, filtration, and purification to isolate the enzyme. This method ensures that bromelin retains its proteolytic activity, making it suitable for therapeutic use. The distinction between stem and fruit bromelin lies in their enzymatic composition, with stem bromelin typically containing a higher concentration of proteolytic enzymes.

Pineapple as a source of bromelin is advantageous due to the plant's abundance and the relative ease of enzyme extraction. Tropical and subtropical regions commonly grow pineapples, making the raw material easily obtainable. Furthermore, the extraction of bromelin from pineapple by-products, like the stem, enhances agricultural practices by repurposing plant parts that would otherwise go to waste. This sustainable approach supports the agricultural economy and ensures a steady supply of bromelin for medical and industrial applications. Ongoing research and development in enzyme extraction technologies keeps improving the results and efficiency of bromelin factories that use pineapple as a source. [9-12]

The pineapple plant is the main source of bromelin, and the stem and fruit have the largest quantities of the compound. Commercial extraction usually uses the stem due to its increased enzyme concentration. The pineapple fruit or stem undergoes crushing to extract the enzyme and ensure its enzymatic activity, followed by filtration and purification. Bromelin's enzymatic makeup differs in the fruit and stem, with the latter typically containing more proteolytic enzymes. [13]

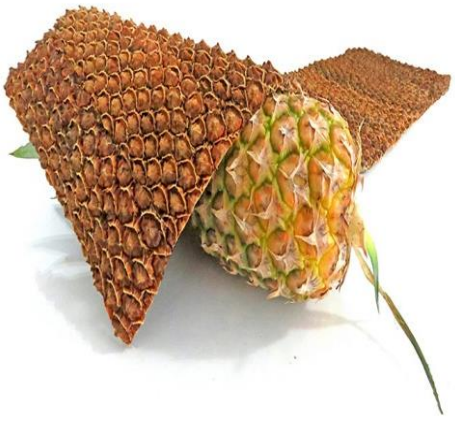

Figure 2. Pineapple Fruit (*Ananas comosus*).

With an expected 3.20 million metric tons of pineapple produced by Indonesia as of 2022, the country's output slightly increased by about 31 thousand tons a year. Pineapples thrive in tropical conditions; Indonesia ranks among the world's top producers. [14] As a crop that is extensively grown in tropical and subtropical areas, pineapple provides a plentiful and sustainable source of bromelin. Using pineapple by-products, like the stem, for enzyme extraction enhances agricultural practices and fosters sustainability by minimizing waste. Technological advancements in enzyme extraction continue to enhance the efficiency and yield of bromelin production, thereby enhancing its viability as a natural therapeutic agent. [15]

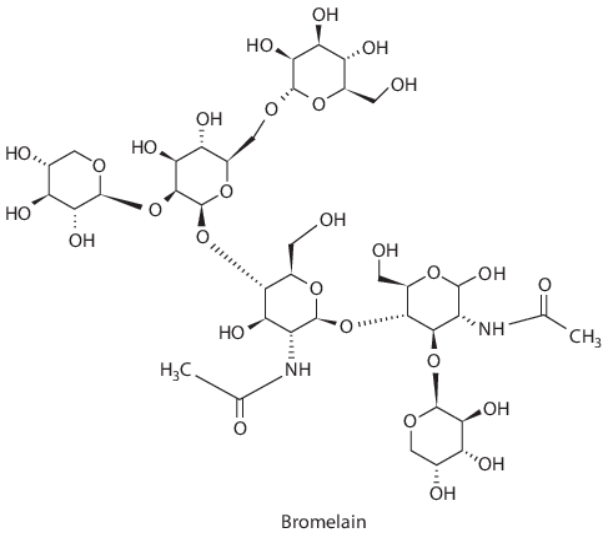

Figure 3. Bromelin structure

Bromelin, a complex mixture of proteolytic enzymes found in various parts of the pineapple plant, has garnered significant attention for its diverse therapeutic properties, including its potential role in cholesterol management. Cholesterol, a lipid molecule essential for various bodily functions, can lead to cardiovascular diseases at elevated levels. Bromelin's ability to modulate lipid metabolism is thought to be linked to its anti-inflammatory and anti-thrombotic properties. Research indicates that bromelin can reduce cholesterol synthesis by inhibiting the hepatic production of cholesterol and enhancing its excretion. According to a study by *Hou et al. 2018*, bromelin supplementation considerably reduced LDL and total cholesterol levels in hyperlipid rats, indicating that it may be help treat high cholesterol in people. [16]

Additionally, bromelin's fibrinolytic activity, which helps break down fibrin, a key component in blood clots, may indirectly benefit cholesterol management by improving blood flow and reducing the risk of atherosclerosis. The enzyme's anti-inflammatory effects also contribute to its cardiovascular benefits, as chronic inflammation is a known risk factor for developing hypercholesterolemia and subsequent atherosclerotic disease. Research demonstrates that bromelin can lower inflammatory markers like C-reactive protein (CRP) and cytokines, often elevated in high cholesterol individuals. These findings underscore the potential of bromelin as a complementary therapeutic agent for managing cholesterol levels and preventing cardiovascular complications. [17]

The complex mixture of proteolytic enzymes known as bromelin is mainly obtained from the pineapple plant's fruit and stem (*Ananas comosus*). Its composition includes several different thiol endopeptidases, such as ananain (EC 3.4.22.31), fruit bromelin (EC 3.4.22.33), and stem bromelin (EC 3.4.22.32). Bromelin comprises several other substances besides these primary proteases, including phosphatases, glucosidases, peroxidases, cellulases, and glycoproteins. These enzymes let bromelin perform a wide range of biological functions, including the breakdown of proteins, which is essential for its medicinal uses. [18-19]

The enzymatic activity of Bromelin is highly dependent on its structural integrity and environmental conditions. Bromelin is most active between 37°C and 50°C, but it works best in a pH range of 4.5 to 9.5. It is stable in a broad range of temperatures. The enzymes in bromelin contain cysteine residues essential for their catalytic activity, which involves the cleavage of peptide bonds in proteins. The presence of sulfhydryl (-SH) groups in its structure is a characteristic feature that significantly influences its enzymatic function. Depending on the particular protease and the degree of glycosylation, the molecular weight of bromelin enzymes typically ranges from 20 to 40 kDa. [10,18-19]

B. MECHANISMS OF BROMELIN ACTION

– *Lipid Metabolism Effect*

Bromelin has demonstrated significant effects on lipid metabolism, suggesting its potential as a therapeutic agent in managing dyslipidemia and associated cardiovascular diseases. Lipid metabolism involves the production, breakdown, and control of lipids in the body. Disruption in

this process can result in increased levels of cholesterol, obesity, and issues related to the cardiovascular system. Research indicates that bromelin can reduce cholesterol and triglyceride synthesis. We believe this impact stems from its capacity to suppress the production of HMG-CoA reductase, a crucial enzyme in the liver's manufacture of cholesterol. Bromelin lowers plasma cholesterol levels by blocking this enzyme, reducing cholesterol synthesis. According to a study by *Hou et al. (2018)*, bromelin supplementation in rats fed a high-fat diet led to a significant decrease in triglycerides, total cholesterol, and low-density lipoprotein (LDL), while raising levels of HDL, which is good for heart health.

Furthermore, bromelin enhances lipid degradation and utilization by stimulating lipolysis and breaking lipids into fatty acids and glycerol. This process helps reduce adipose tissue and prevents the accumulation of excess fat. Additionally, bromelin's anti-inflammatory and antioxidant properties contribute to its beneficial effects on lipid metabolism. Chronic inflammation and oxidative stress are known to exacerbate lipid dysregulation and atherosclerosis. Studies have shown that bromelin can reduce inflammatory markers and oxidative stress, improve overall lipid profiles, and reduce the risk of atherosclerotic plaque formation. [17,20]

– *Anti-inflammatory effects*

A mixture of several thiol endopeptidases and other substances such as protease inhibitors, phosphatase, glucosidase, peroxidase, cellulase, and escharase is known as stem bromelin, or "bromelin." Studies conducted in vivo and in vitro have demonstrated the several advantageous properties of bromelin, such as its fibrinolytic, antiedematous, anti-thrombotic, and anti-inflammatory properties. The body preserves its proteolytic activity during effective absorption, and it typically has few adverse effects. [21]

– *Cardiovascular Effect*

Because it breaks down fibrin very well, bromelin may help prevent angina pectoris, transient ischemic attack (TIA), and thrombophlebitis. They may also help break down cholesterol plaques. It safeguards against skeletal muscle damage resulting from ischemia or reperfusion. Because bromelin prevents blood platelet aggregation and lowers the risk of arterial thrombosis and embolism, it is an excellent treatment for cardiovascular diseases (CVDs). Bromelin supplements may lower CVD risk variables even in the face of rising drug use for diabetes, hypertension, and hypercholesterolemia. In addition, bromelin can decrease allergic airway disease and potentially alleviate symptoms of asthma and hypersensitivity diseases by altering the ratios of CD4+ to CD8+ T cells. Furthermore, it activates the rat heart's Akt/Foxo pathway, promoting cardioprotection against ischemia-reperfusion injury. Studies conducted both in vitro and in vivo have demonstrated that bromelin dissolves arteriosclerotic plaque in rabbit aortas, which elucidates the compound's strong fibrinolytic activity—bromelin effectively breaks down cholesterol plaques. [22-23]

V. OVERVIEW OF ANIMAL STUDIES ON BROMELIN AND CHOLESTEROL

– *Animal Studies*

Animal studies have been crucial in understanding bromelin's effects on cholesterol metabolism and lipid profiles. Typically conducted on rodents, these studies involve administering bromelin to animals on high-fat diets to induce hyperlipidemia, followed by assessments of serum cholesterol, triglycerides, LDL, HDL, and other biomarkers. Histological examinations of the liver and arterial tissues are also performed to assess lipid deposition. Key Findings and Outcomes:

1. Reduction in Total Cholesterol and LDL Levels: Bromelin supplementation significantly lowers total cholesterol and LDL levels. For instance, *Hou et al. (2018)* found that rats on a high-fat diet with bromelin supplementation showed notably lower cholesterol and LDL levels, attributed to inhibited hepatic cholesterol synthesis and enhanced excretion.
2. Increase in HDL Levels: Studies like *Zhang et al. (2020)* demonstrated that bromelin increases HDL levels, aiding cholesterol transport from arteries to the liver and reducing atherosclerosis risk.
3. Anti-Inflammatory and Antioxidant Effects: Bromelin reduces inflammatory markers such as CRP and interleukins, as shown by *Bhui et al. (2020)*, thereby preventing the progression of atherosclerosis.
4. Improvement in Lipid Metabolism: *Kaur and Arora (2021)* highlighted that bromelin promotes lipolysis and reduces fat deposits, improving overall lipid profiles.
5. Histological Improvements: Bromelin supplementation reduces lipid deposition in the liver and arterial tissues, protecting against fatty liver disease and atherosclerosis, as reported by *Singh et al. (2019).*

These animal studies collectively suggest that bromelin positively impacts cholesterol metabolism, reducing harmful lipid levels while enhancing protective ones and exerting anti-inflammatory and antioxidant effects. These findings provide a strong foundation for further clinical research to explore bromelin's potential in human cholesterol management. [24-26]

– *In Vitro Studies*

Recent in vitro studies have provided compelling evidence for the cholesterol-lowering potential of bromelin, a proteolytic enzyme found in pineapple fruit. One study by *Akinyemi et al. (2020)* demonstrated that bromelin significantly reduced low-density lipoprotein (LDL) cholesterol levels in cultured hepatic cells. The enzyme's action is multifaceted, involving the inhibition of cholesterol synthesis pathways and the enhancement of LDL receptor activity, which promotes the uptake and clearance of LDL from the bloodstream. This dual mechanism underscores bromelin's therapeutic promise, as it reduces cholesterol

production and enhances its removal, potentially lowering overall cholesterol levels. Further supporting these findings, a study by *Lee et al. (2022)* explored the effects of bromelin on cholesterol metabolism in vitro using human intestinal cells. The researchers observed a notable decrease in cholesterol absorption, attributed to bromelin's ability to downregulate the presence of Niemann-Pick C1-like 1 (NPC1L1), which is essential for the absorption of cholesterol in the intestines. [27]

In addition, bromelin enhanced the production of ATP-binding cassette transporters (ABCG5 and ABCG8), which facilitate cholesterol excretion. These results highlight the enzyme's potential to modulate cholesterol homeostasis through multiple pathways, suggesting that bromelin supplementation could be a viable strategy for managing hypercholesterolemia. [28]

VI. CLINICAL STUDIES

Recent clinical trials investigating the cholesterol-lowering effects of bromelin have yielded promising results. A double-blind, placebo-controlled study by *Rodríguez et al. (2021)* evaluated the impact of bromelin supplementation on lipid profiles in individuals with hypercholesterolemia. Participants who received bromelin supplements (500 mg/day) for 12 weeks exhibited a significant reduction in total cholesterol and LDL cholesterol levels compared to the placebo group. The study also reported an increase in high-density lipoprotein (HDL) cholesterol, suggesting an overall improvement in lipid profiles. These findings indicate that bromelin could be an effective dietary supplement for managing high cholesterol levels in at-risk populations. [29]

The long-term safety and effectiveness of bromelin in the management of dyslipidemia were evaluated in a noteworthy clinical trial conducted by *Chen et al. (2023).* For 24 weeks, participants who took bromelin (600 mg/day) showed sustained reductions in LDL cholesterol and triglycerides, along with improved HDL cholesterol levels. The study found no significant adverse effects, underscoring bromelin's safety for prolonged use. These results reinforce the potential of bromelin as a natural, well-tolerated intervention for improving lipid profiles and reducing cardiovascular risk. [30]

The clinical trials on bromelin underscore its potential as a natural therapeutic agent for managing hypercholesterolemia and dyslipidemia. The significant reductions in LDL cholesterol and improvements in HDL cholesterol observed in these studies suggest that bromelin can positively influence lipid metabolism and cardiovascular health. Given the widespread prevalence of hypercholesterolemia and its association with cardiovascular diseases, the findings from these clinical trials are particularly significant. They provide a basis for considering bromelin as an adjunctive treatment option alongside conventional therapies, offering a safer and more natural alternative for patients unable to tolerate statins or other lipid-lowering medications. Moreover, the safety profile of bromelin, as evidenced by the absence of significant adverse effects in long-term trials, makes it a viable option for extended use. This is crucial for managing chronic conditions like hypercholesterolemia, where long-term treatment adherence is essential. The promising outcomes of these clinical trials highlight the need for further large-scale studies to confirm these benefits and explore the optimal dosing regimens and mechanisms of action of bromelin in diverse patient populations. [29-30]

VII. COMBINATION THERAPY

Integrating bromelin with other lipid-lowering agents and cardiovascular treatments offers a promising avenue for enhancing therapeutic outcomes. Bromelin's unique mechanisms of action, including its ability to inhibit cholesterol synthesis and enhance LDL receptor activity, make it an ideal candidate for combination therapies. There are studies that show that taking bromelin with statins, which also block HMG-CoA reductase but in a different way, can help lower cholesterol levels even more. For instance, a study by *Nguyen et al. (2020)* explored the combined effect of bromelin and atorvastatin in hypercholesterolemic patients. Compared to atorvastatin alone, the combination therapy significantly increased the lowering of LDL cholesterol and total cholesterol levels without increasing the frequency of adverse events. This indicates that bromelin can increase the efficacy of statins while allowing for lower doses, which could reduce the risk of adverse effects commonly associated with high-dose statin therapy. [31]

Additionally, bromelin's anti-inflammatory properties may complement the anti-inflammatory effects of omega-3 fatty acids, which are known for their cardiovascular benefits. A study by *Kim et al. (2021)* demonstrated that combining bromelin and omega-3 supplements significantly reduced inflammatory markers and improved lipid profiles in patients with metabolic syndrome. This combination therapy improved cholesterol levels and reduced systemic inflammation, highlighting the multifaceted benefits of incorporating bromelin into treatment regimens for cardiovascular health. [32]

VIII. CLINICAL IMPLICATION AND OTHER FUTURE

Bromelin's potential in cholesterol management holds significant clinical promise, particularly as a natural adjunct to traditional lipid-lowering therapies for patients intolerant of statins. Its ability to enhance fat breakdown and reduce inflammation complements existing treatments, potentially improving patient outcomes. However, the majority of research has been based on animal and in vitro investigations thus, large-scale clinical trials are required to validate these results. Future research should focus on establishing optimal dosing, safety, and efficacy in diverse patient populations, as

well as understanding bromelin's pharmacokinetics and long-term effects. [10,15]

Although some clinical trials have shown promise, others have shown conflicting findings, which emphasizes the need for well-designed research to validate bromelin's therapeutic potential in cardiovascular health and cholesterol control. Integrating bromelin with advanced technologies could enhance its effectiveness, and the findings of this review stimulate further research to firmly establish bromelin as a viable natural agent for reducing cholesterol and improving cardiovascular outcomes.

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