The Role of Natural Compounds for Atherosclerosis Treatment: Lessons Learned from The Use of Curcumin

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Abstract

Relationships between the occurrence of various diseases that have certain similarities are of particular interest to scientists and clinicians. On the one hand, such an analysis can help to better understand the underlying mechanisms and, on the other hand, to cope with the disease/diseases more effectively. In this review, we look at the relationship between NAFLD and atherosclerosis. The main and obvious intersection in their pathogenesis is, of course, lipid metabolism disorders. However, this is not the only relationship. In addition to the similarity of pathogenesis, we considered the possibility of one disease to serve as a risk factor for the development of the second. We devoted a separate chapter to the methods of treatment of these two pathologies.

Keywords: Curcumin; Natural compound; Phytotherapy; Atherosclerosis; Cardiovascular disease.

Significance | Curcumin has various pharmacological effects on atherosclerosis. This review discussed the promising therapeutic potential, of curcumin as anti-inflammatory, lipid regulation, and endothelial function for cardiovascular disease.

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Introduction

Contemporary statistics shows that one of the most common causes of death in the world is cardiovascular disease, in particular, atherosclerosis, diagnosed in more than ten percent of the world's population. This disease is characterized by a complex pathogenesis, which includes disorders of lipid exchange, the formation of atherosclerotic plaques, thrombosis and inflammatory processes (Zhu et al., 2020). In the therapy of atherosclerosis, as in other cardiovascular diseases, therapeutic agents affecting one or more specific pathogens are widely used. However, a number of studies have noted that diets and natural nutrients can be even more effective due to their multifactorial effects on the body and pathogenic factors (Khan & Rahmatullah, 2024). One such natural nutrient known since ancient times is curcumin. Before extensive scientific research, curcumin was used in ancient China as an anti-inflammatory and general tonic (Ziółkiewicz et al., 2023). Modern research shows that curcumin has antioxidant and antitumor properties, so it can have a significant beneficial effect on tumor necrosis factor. However, some studies do not support a significant effect of this nutrient on the pathogenesis of CVD: for example, no significant therapeutic effects were achieved in a mouse model of atherosclerosis. This means that the mechanism of action of curcumin, as well as its therapeutic efficacy, are still subject to study and further analysis (Hewlings and Kalman, 2017).

The review critically analyzes the current scientific understanding of curcumin's mechanisms of action in atherosclerosis, highlighting

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its anti-inflammatory, antioxidant, and lipid-lowering properties. It synthesizes findings from in vitro and in vivo studies, showcasing curcumin's ability to modulate key cellular processes involved in atherosclerosis development, such as endothelial dysfunction, smooth muscle cell proliferation, and foam cell formation.

Furthermore, the review synthesizes evidence from clinical trials exploring the effects of curcumin supplementation on various cardiovascular risk factors and outcomes. It discusses the challenges associated with curcumin's bioavailability and identifies potential strategies to enhance its efficacy, such as novel drug delivery systems and structural modifications.

Ultimately, the review concludes by underscoring the promising role of curcumin as a therapeutic agent for atherosclerosis and other cardiovascular diseases. It calls for further research, including large-scale clinical trials, to fully elucidate curcumin's mechanisms of action and optimize its clinical utility in preventing and treating atherosclerosis and related conditions.

Curcumin Overview

Many human diseases like cancer, neurological disorders, cardiovascular diseases (CVD), and atherosclerosis are complex and involve multiple genes and factors, limiting the efficacy of single-target drugs (Leopold and Loscalzo, 2018). Nutraceuticals, such as curcumin, are key in addressing these challenges. Curcumin, known for its multitarget effects and minimal side effects, acts on various pathways and receptors simultaneously (Amalraj, et al., 2016).

Historical Use and Therapeutic Potential

Historical records of using turmeric for health date back to 1748, with the first documented use of curcumin in human diseases in 1937 (Gupta et al., 2013). Studies have showcased curcumin's diverse therapeutic benefits, including anti-inflammatory, hypoglycemic, antioxidant, wound healing, and antimicrobial properties (Sharifi-Rad et al., 2020; Benameur et al., 2023; Simental-Mendía et al., 2019). Clinical research supports its efficacy in managing various conditions like CVD, liver disease, chronic arsenic exposure, and alcohol intoxication. Curcumin can be used independently or in conjunction with other substances for enhanced effects (Smirnova et al., 2023).

Mechanisms of Action and Modulation Effects

Curcumin's pleiotropic nature has attracted attention due to its ability to influence numerous cellular signaling molecules involved in inflammation, apoptosis, antioxidant defense, and metabolic pathways (Fessler et al., 2023). Studies have highlighted its modulating effects on key factors related to disease progression.

Bioavailability Challenges and Solutions:

Despite its therapeutic potential, curcumin faces challenges with low bioavailability due to poor absorption, rapid metabolism, and excretion. Strategies like combining curcumin with piperine to inhibit metabolic pathways have been successful in enhancing bioavailability (Sohn et al., 2021; Prasad et al., 2014). Innovations like phytosomal curcumin complexes and nanoparticle formulations have shown promising results in improving curcumin absorption and efficacy (Tabanelli et al., 2021).

Anti-Inflammatory Mechanism of Curcumin

Inflammation is a complex process involving various steps in the body's response to stimuli. Curcumin exhibits anti-inflammatory properties that aid in regulating this response by targeting key signaling pathways and decreasing the production of inflammatory substances (Chen et al., 2017).

Curcumin interacts with specific receptors in the body, notably Toll-like receptors, which, in turn, modulate crucial signaling pathways like NF-κB and MAPK to manage inflammation. It can also impact other pathways, such as JAK/STAT, to further adjust the inflammatory response (Burge et al., 2019).

A significant target of curcumin is the NLRP3 inflammasome, a complex linked to inflammatory diseases. By inhibiting this complex or related pathways, curcumin assists in alleviating inflammation (Mazidi et al., 2016).

Research indicates that curcumin can decrease inflammatory mediators in both animal and human studies. Clinical trials have shown improvements in plasma markers associated with inflammation when curcumin is administered (Huang et al., 2021; Hassaniazad et al., 2021).

Curcumin's capacity to regulate immune cells like dendritic cells, T helper cells, and T regulatory cells helps maintain the equilibrium between pro-inflammatory and anti-inflammatory responses. By influencing pathways like IL-23/Th17, curcumin aids in regulating this balance and promoting immune homeostasis (Makuch et al., 2021).

Furthermore, curcumin's antioxidant properties are essential in reducing oxidative stress, which is closely linked to inflammation. By inhibiting the generation of reactive oxygen species and enhancing antioxidant enzyme activity, curcumin aids in mitigating inflammation and its detrimental effects (Handono et al., 2015; Chauhan and Zennadi, 2023).

Effect of Curcumin on Atherosclerosis

Murine Models Insights

Studies in mouse models indicate that curcumin administration effectively reduces atherosclerosis development and progression without affecting lipid levels (El Hadri et al., 2021). Additionally, gene expression alterations linked to leukocyte adhesion and transendothelial migration were observed in response to curcumin treatment (Baratzadeh et al., 2022; Meng et al., 2019; Feng et al., 2019).

Foam Cell Formation Regulation

Curcumin showcases the ability to regulate cholesterol homeostasis in macrophages, resulting in reduced foam cell formation and decreased occurrence of atherosclerosis (Li et al., 2014). The

modulation of scavenger receptor activity and cholesterol efflux pathways by curcumin contributes to a reduction in macrophage lipid accumulation, a hallmark of early atherosclerotic lesions (Figure 1) (Zhao et al., 2018).

Inflammatory Response Inhibition

In various studies conducted on LDLR-/- mice, curcumin demonstrated significant anti-inflammatory effects and suppressed critical factors involved in foam cell formation, contributing to the reduction of atherosclerosis and fatty liver disease (Lin et al., 2015). Curcumin's ability to inhibit pro-inflammatory cytokine production and NF-κB signaling not only attenuates local inflammation within atherosclerotic plaques but also exerts systemic anti-inflammatory effects (Chen et al., 2021; Hasan et al., 2014).

Enhancing Endothelial Function

Pre-treatment with curcumin enhances endothelial function by reducing monocyte adhesion and endothelial permeability through mechanisms involving the inhibition of adhesion-related genes and reactive oxygen species (ROS) (Ma et al., 2017). By promoting endothelial integrity and reducing endothelial activation, curcumin may prevent the initial steps that lead to atherosclerotic plaque formation and progression (Figure 2) (Alidadi et al., 2021).

Targeting Smooth Muscle Cells (SMCs)

Curcumin effectively inhibits smooth muscle cell migration, proliferation, and collagen production in experimental models, offering promise in addressing arterial injury-induced neointima formation (Zhang et al., 2022). Through the modulation of key signaling pathways involved in SMC function and phenotypic switching, curcumin may help prevent excessive vascular smooth muscle cell proliferation and migration that contribute to atherosclerosis progression (Lu et al., 2018).

Mechanistic Insights in Human SMCs

For human aortic smooth muscle cells (SMCs), curcumin inhibits migration induced by TNF-α, blocks NF-κB translocation, prevents MMP-9 activation, and induces nucleolar stress through SIRT7 downregulation (He et al., 2021). These findings suggest that curcumin's anti-atherosclerotic effects are not limited to animal models but also extend to human vascular cells, highlighting its translational potential in combating atherosclerosis in clinical settings (Qin et al., 2017).

Cholesterol Regulation and Cell Cycle Arrest

Curcumin demonstrates the ability to inhibit cholesterol accumulation induced by oxidized LDL in rat SMCs, suppresses SREBP-1 nuclear translocation, promotes caveolin-1 expression, and induces cell cycle arrest via p53 stabilization (Yu and Lin, 2010; Preusch et al., 2010; Bielak-Zmijewska et al., 2019). By targeting key regulators of cholesterol metabolism and cell cycle progression, curcumin may help maintain SMC quiescence and prevent their aberrant proliferation in response to atherosclerosis-related stimuli (Cao et al., 2017).

The multifaceted actions of curcumin in modulating various cell types and pathways involved in atherosclerosis underscore its potential as a versatile therapeutic agent for combating this prevalent cardiovascular disease (Lewinska et al., 2015; Zeng et al., 2022).

Clinical Studies of Curcumin

Only a small number of clinical trials have been conducted, including double-blind placebo-controlled studies and randomized controlled trials. A 12-week randomized placebo-controlled trial involving 118 participants found that curcumin treatment reduced the risk of acute cardiovascular events in people with type 2 diabetes and dyslipidemia (Różański et al., 2023). Another randomized controlled trial with 87 patients found that 1 g curcumin for 8 weeks reduced total cholesterol (TC), triglyceride (TG) and high-density lipoprotein cholesterol (HDL-c) levels in patients with non-alcoholic fatty liver disease. Curcumin has been shown to be a powerful antioxidant. In contrast, curcumin reduced low-density lipoprotein cholesterol (LDL-c) and apolipoprotein B (Apo B) and increased apolipoprotein A1 (Apo A1) and HDL-c levels in healthy individuals, indicating its possible efficacy against atherosclerosis (Wongcharoen et al., 2012). In coronary artery bypass grafting, 4 g/day curcumin reduced the incidence of acute myocardial infarction and significantly lowered malondialdehyde levels. Furthermore, in patients with chronic obstructive pulmonary disease, curcumin (Seracurmin®) at a dose of 90 mg/day for 24 weeks reduced the concentration of α1-antitrypsin-low-density lipoprotein (AT-LDL) complex, a known factor in atherosclerosis (Kunnumakkara et al., 2017). Another randomized trial showed that curcumin supplementation at a daily dose of 80 mg improved dyslipidemia by reducing serum TG, salivary amylase and beta-amyloid levels and increasing plasma nitric oxide levels after four weeks of treatment. Similarly, in a double-blind, placebo-controlled study, 200 mg curcumin supplementation improved endothelial function as measured by flow-mediated dilation (FMD), thereby reducing the risk of cardiovascular disease (Alidadi et al., 2021). In another pilot study, curcumin at a dose of 500 mg/day for 12 weeks reduced arterial stiffness in young obese men with aortic stiffness. It is important to note that studies involving curcumin have limitations, such as small sample sizes, which emphasize the need for large-scale clinical trials to fully explore the potential of curcumin and identify specific molecular targets of curcumin in the treatment of atherosclerosis (Surma et al., 2022).

Limitations

The review on the role of natural compounds for atherosclerosis treatment, focusing on curcumin, provides an in-depth analysis of the potential therapeutic benefits of curcumin in addressing the multifactorial nature of atherosclerosis. However, it is important to

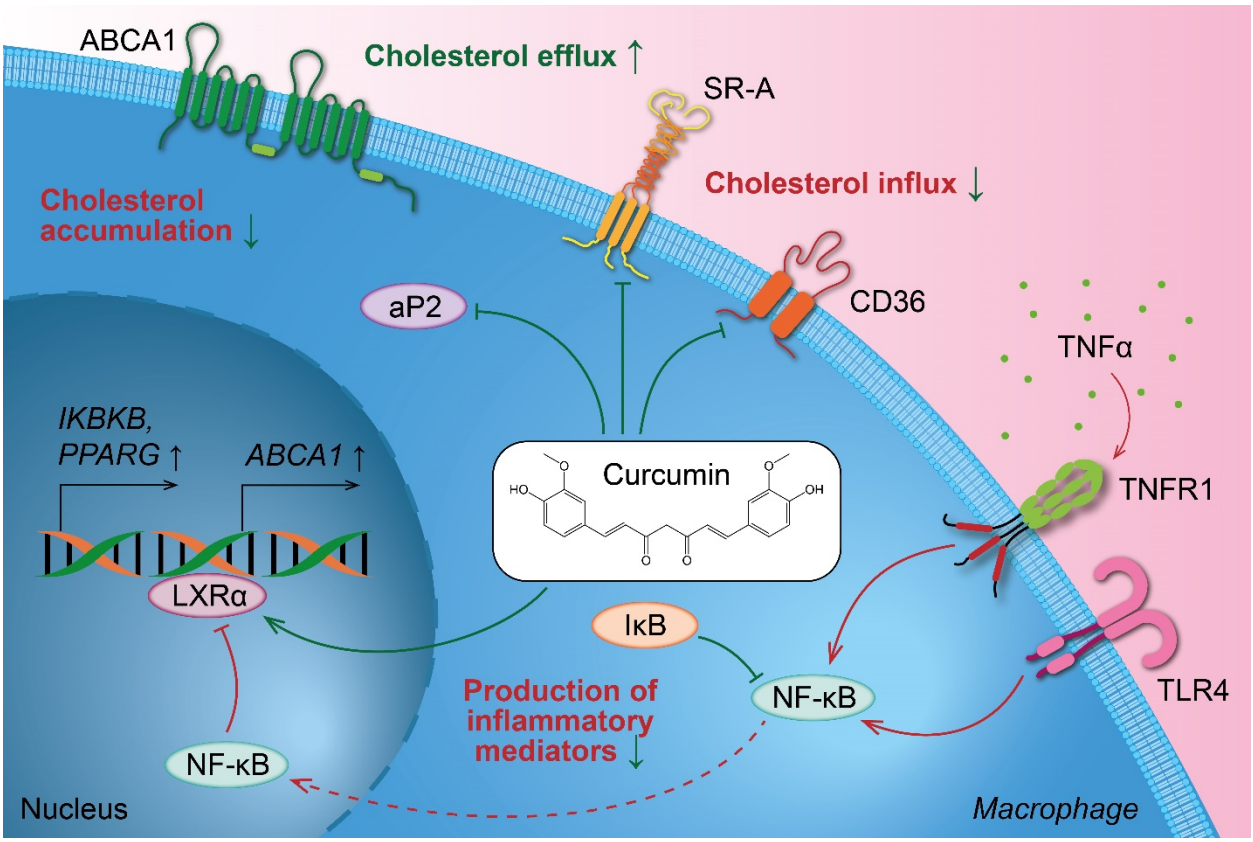

Figure 1. Effect of Curcumin on Macrophages. Curcumin may modulate macrophage function in several ways: 1) Anti-inflammatory effects: Curcumin has been shown to inhibit the production of pro-inflammatory molecules such as cytokines in macrophages; 2) Immune response modulation: Curcumin may regulate macrophage activity in response to pathogens or pro-inflammatory modulators, potentially influencing the clearance of pathogens and the immune defense against infections; 3) Cholesterol metabolism: Curcumin can influence the expression of genes involved in cholesterol uptake, efflux, and storage, thereby impacting the balance of cholesterol within these immune cells; 4) Inhibition of foam cell formation: Curcumin has been shown to inhibit the transformation of macrophages into foam cells by preventing or reducing intracellular lipid accumulation.

Abbreviations: ABCA1 – ATP Binding Cassette Subfamily A Member 1; aP2 – Fatty Acid Binding Protein; CD36 – Cluster of Differentiation 36 or Scavenger Receptor Class B Member 3; IKBKB – gene encoding Inhibitor of Nuclear Factor Kappa B Kinase Subunit Beta; IκB – Inhibitor of Nuclear Factor Kappa B; LXRα – Liver Receptor X-α; NF-κB – Nuclear Factor Kappa B; PPARG – Peroxisome Proliferator Activated Receptor Gamma; SR-A – Macrophage Scavenger Receptor Class A; TLR4 – Toll Like Receptor 4; TNFR1 – Tumor Necrosis Factor Receptor 1; TNFα – Tumor Necrosis Factor α.

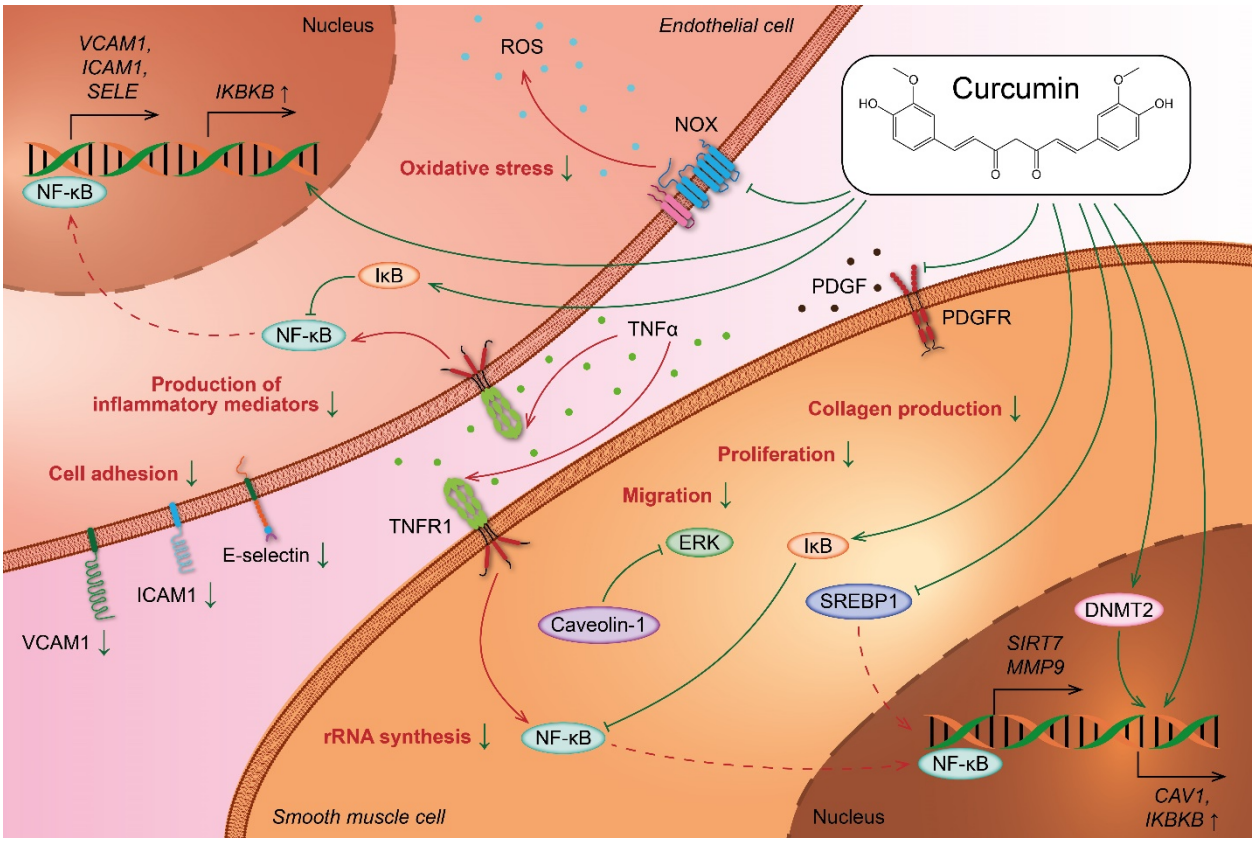

Figure 2. Effect of Curcumin on Endothelial and Smooth Muscle Cells. Curcumin has shown various effects on endothelial and smooth muscle cells: 1. Endothelial cells: A) Anti-inflammatory effects: Curcumin has been shown to reduce inflammation within endothelial cells by inhibiting the expression of inflammatory mediators and adhesion molecules. B) Antioxidant properties: Curcumin possesses antioxidant capabilities that can help protect endothelial cells from oxidative stress, which is a contributing factor to endothelial dysfunction. 2. Smooth muscle cells: A) Inhibition of proliferation: Curcumin has been found to inhibit the excessive growth and proliferation of smooth muscle cells. B) Anti-contractile effects: Some research suggests that curcumin may exert anti-contractile effects on smooth muscle cells, potentially influencing vascular tone and reactivity. C) Modulation of extracellular matrix production: Curcumin has been shown to influence the production of extracellular matrix components in smooth muscle cells, which may have implications for vascular remodeling and repair processes.

Abbreviations: CAV1 – gene encoding Caveolin-1; DNMT2 – DNA Methyltransferase 2; ERK – Extracellular Signal-Regulated Kinase; ICAM1 – Intercellular Adhesion Molecule 1; IKBKB – gene encoding Inhibitor of Nuclear Factor Kappa B Kinase Subunit Beta; IκB – Inhibitor of Nuclear Factor Kappa B; MMP-9 – Matrix metallopeptidase 9; NF-κB – Nuclear Factor Kappa B; NOX – NADPH oxidase; PDGF – Platelet-Derived Growth Factor; PDGFR – Platelet-Derived Growth Factor Receptor; ROS – Reactive Oxygen Species; SELE – gene encoding Selectin E; SIRT7 – Sirtuin 7; SREBP1 – Sterol Regulatory Element-Binding Protein 1; TNFR1 – Tumor Necrosis Factor Receptor 1; TNFα – Tumor Necrosis Factor α; VCAM1 – Vascular Cell Adhesion Molecule 1.

critically examine the methodology of clinical trials mentioned in the review and consider potential biases that could impact the interpretation of results.

Sample Size and Study Design: Many of the clinical trials discussed in the review have relatively small sample sizes, which can limit the generalizability of the findings. Studies with larger sample sizes are generally more robust and provide stronger evidence for the efficacy of interventions like curcumin. Additionally, the use of randomized controlled trials (RCTs) with adequate blinding and appropriate control groups is essential to minimize bias and ensure the reliability of results.

Biases and Confounding Variables: It is essential to consider potential biases in clinical trials, such as selection bias, measurement bias, and confounding variables that could impact the outcomes. For example, the lack of blinding or placebo control in some trials could introduce bias into the results. Moreover, the presence of confounding variables, such as concomitant medications or lifestyle factors, needs to be carefully accounted for in the data analysis.

Publication Bias: There is a risk of publication bias in the review if only studies with positive results are included, while studies with neutral or negative findings are omitted. Publication bias can skew the overall interpretation of the efficacy of curcumin in atherosclerosis treatment. A comprehensive literature search and inclusion of all relevant studies, regardless of their outcomes, is crucial to mitigate this bias.

Heterogeneity of Studies: Clinical trials often vary in terms of study populations, intervention doses, duration of treatment, and outcomes assessed. The heterogeneity among studies can make it challenging to draw definitive conclusions about the efficacy of curcumin in atherosclerosis treatment. Meta-analyses or systematic reviews that account for this heterogeneity can provide a more comprehensive overview of the available evidence.

Potential Conflicts of Interest: It is essential to consider any potential conflicts of interest that could influence the design, conduct, or reporting of clinical trials evaluating curcumin. Industry sponsorship or financial ties to the manufacturers of curcumin supplements could introduce bias in the study results. Transparency in disclosing conflicts of interest is crucial for maintaining the integrity of the research findings.

Conclusions and Perspectives

Considerable experimental evidence suggests that curcumin exhibits preventive effects against endothelial dysfunction, smooth muscle cell proliferation and migration, and foam cell formation, while also modulating macrophage polarization. Additionally, curcumin counteracts the inflammatory response, thereby supporting its potential use in the treatment of atherosclerosis. The anti-atherosclerotic properties of curcumin are attributed to its ability to suppress inflammation by shifting macrophage polarization from M1 to M2 or by inducing M2 polarization through the regulation of TLR4/MAPK/NF-κB pathways in macrophages and the secretion of interleukins (IL-4 and/or IL-13). Likewise, curcumin regulates the expression and activity of lipid transporters (CD36, CD38, ABCA1, aP2, etc.) responsible for cholesterol uptake and efflux, thereby maintaining cellular homeostasis. Furthermore, curcumin reduces the circulating levels of ox-LDL and inhibits oxLDL-induced pro-atherogenic events by decreasing the expression of MCP-1 and THBS-4 through the p38 MAPK and NF-κB pathways. Similarly, curcumin suppresses TLR4 expression and macrophage infiltration in aortic tissues, providing protection against the formation of atherosclerotic plaques. Recent research has also suggested that curcumin blocks LPA-induced MCP-1 expression via the TGFBR1/ROCK signaling pathway. Further studies are necessary to enhance our understanding of the mechanism(s) of action of curcumin against atherosclerosis, particularly in clinical settings. Moreover, the development of novel drug delivery systems, such as curcumin nanomicelles, is crucial for improving its oral bioavailability, which may contribute to its clinical effectiveness.

Curcumin is a versatile compound with various therapeutic applications in cancer, neurological disorders, chronic inflammatory diseases, and cardiovascular diseases (CVDs). This review highlights the crucial role of curcumin in protecting both humans and animals from cardiovascular dysfunction, which is a primary step in the development of CVDs, including atherosclerosis, aortic aneurysm, myocardial infarction (MI), and stroke. Its antioxidant, anti-inflammatory, and anti-apoptotic properties have been reported to effectively improve cardiac hypertrophy, heart failure, diabetic cardiovascular complications, and cardiotoxicity. Extensive in vitro and in vivo investigations have elucidated the potential mechanisms of action, and some of these effects have also been validated through clinical trials. Although curcumin has been considered "generally regarded as safe" by the US Food and Drug Administration (CFR, 2017) due to its safety and efficacy in human clinical trials, its clinical use has been limited by its low bioavailability, primarily caused by poor absorption and rapid metabolism. To overcome this limitation, researchers have explored various curcumin formulations and suggested appropriate drug combinations. Additionally, structural modifications of curcumin have led to the discovery of synthetic derivatives with better bioavailability, some of which demonstrate comparable or superior pharmacokinetic and pharmacodynamic profiles compared to curcumin itself. However, toxicological data on these derivatives are currently lacking. As a food component, curcumin is well-tolerated, and its safety has been demonstrated even at doses up to 12 g/day. Consequently, curcumin may become a routine food supplement, similar to vitamins and fish oil, for the

prevention and treatment of CVDs. Nevertheless, further studies and clinical trials with larger sample sizes and optimized dosages are required to validate the current findings regarding the prevention and treatment of CVDs.

Determining the optimal dosage of curcumin is essential to ensure its effectiveness while minimizing potential side effects. Studies have shown that curcumin's bioavailability is limited due to its poor absorption and rapid metabolism, necessitating higher doses for therapeutic effects. However, the exact optimal dosage of curcumin for the prevention and treatment of atherosclerosis and other cardiovascular diseases needs further investigation through robust clinical trials.

To address the challenges related to curcumin's poor bioavailability, researchers have explored various strategies to enhance its absorption and efficacy. These strategies include the development of novel drug delivery systems such as curcumin nanomicelles, which have shown promise in improving oral bioavailability. Further research into these delivery systems and other formulation approaches is crucial to optimizing curcumin's bioavailability and enhancing its clinical effectiveness.

While curcumin has been generally regarded as safe by regulatory authorities, including the US Food and Drug Administration, long-term safety profiles need to be thoroughly investigated, especially at higher doses. Clinical trials have demonstrated the safety of curcumin even at doses up to 12 g/day, suggesting its potential as a routine food supplement for the prevention and treatment of cardiovascular diseases. However, ongoing monitoring of potential side effects and interactions with other medications is necessary to ensure its long-term safety and efficacy.

In conclusion, determining the optimal dosages, exploring bioavailability enhancement strategies, and assessing the long-term safety profiles of curcumin are crucial steps in harnessing the full therapeutic potential of this natural compound in the prevention and treatment of cardiovascular diseases like atherosclerosis. Further research and clinical trials are needed to establish evidence-based guidelines for the use of curcumin in clinical settings and to address current challenges related to its bioavailability and long-term safety.

Author contribution

A.V.P. conceptualized, V.Y.G., V.N.S., A.N.O., R.V.G. wrote, drafted, reviewed, edited, V.A.K. prepared the graph of the article. All authors have read and agreed to the published version of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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