



TARGETING INFLAMMATION IN ATHEROSCLEROSIS: INSIGHTS FROM NATURAL AND CONVENTIONAL THERAPIES

Vishal Kumar Soni¹, Prateek Singh², and Prashant Kumar Singh^{2*}

¹Indira Gandhi National Open University, Regional Centre Rajkot, Gujarat, India.

²Department of Biochemistry, University of Lucknow, Lucknow, Uttar Pradesh, India.

***Corresponding Author:** Prashant Kumar Singh

*Department of Biochemistry, University of Lucknow, Lucknow, U.P. India,
Email: prashantcdri@gmail.com

Vishal Kumar Soni, Indira Gandhi National Open University,
Regional Centre Rajkot, Gujarat, India

Prateek Singh, Department of Biochemistry, University of Lucknow, Lucknow, U.P. India

Abstract

Atherosclerosis, a cardiovascular disease is known to be one of the major causes of mortality across the globe. It has been predicted that within few years atherosclerosis will be responsible for much greater number of worldwide mortalities. Cardiovascular disease accounts for primary number of all deaths in North America and European countries [1]. Atherosclerosis is derived from the Greek words 'athero' meaning paste and 'sclerosis' which means hardening. Atherosclerosis is a multifactorial disease characterized by immune-inflammatory processes and lipid deposition in arterial walls, leading to plaque formation and progressive narrowing of blood vessels [2]. This pathology is a major cause of coronary artery disease, myocardial infarction, and stroke. While elevated low-density lipoprotein cholesterol (LDL-C), hypertension, and smoking are established risk factors, emerging contributors such as poor sleep, sedentary lifestyle, microbiome imbalance, environmental pollutants, and psychological stress are increasingly recognized. Together, these factors accelerate plaque growth, vascular dysfunction, and thrombus formation, culminating in severe cardiovascular events.

Therapeutic approaches for atherosclerosis target both lipid accumulation and inflammation. Natural compounds like Secoisolariciresinol Diglucoside (SDG), flaxseed lignans, flavonoids (quercetin, anthocyanins), and the medicinal plant *Sphaeranthus indicus* demonstrate lipid-lowering, antioxidant, and anti-inflammatory effects. Canakinumab, an anti-inflammatory biologic, and Ninjurin1 (NINJ1), a novel immune modulator, show promise as emerging targets. Alongside these, conventional drugs such as nifedipine, ramipril, and perindopril remain critical in managing blood pressure and reducing cardiovascular risk.

This review emphasizes the interplay of traditional and non-traditional risk factors in atherosclerosis while outlining both established and innovative therapeutic strategies aimed at reducing disease burden and improving cardiovascular outcomes.

Keywords: Inflammation, Atherosclerosis, Natural Products, Clinical trials

Mechanistic pathways and interconnections among atherosclerosis risk factors

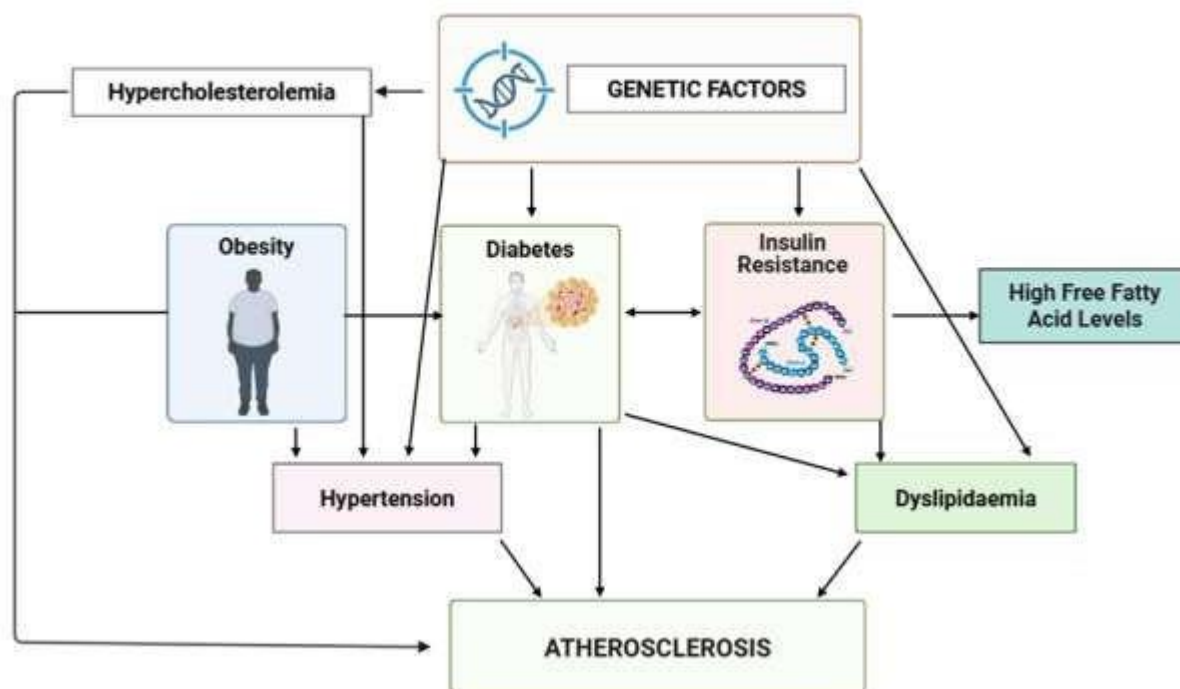


Figure 1: Mechanistic pathways and interconnections among atherosclerosis risk factors

1. Inflammation and initiation of Atherosclerosis

Inflammation is a central driver of atherosclerosis, beginning with endothelial activation that promotes monocyte recruitment, their differentiation into macrophages and foam cells, and the release of pro-inflammatory cytokines. Pyroptosis, a caspase-dependent form of programmed cell death mediated by gasdermin D, further amplifies this response by inducing cell lysis and cytokine release. While initially described as an antimicrobial defense, pyroptosis is increasingly recognized in chronic inflammatory disorders and is now linked to vascular pathology, including early atherogenesis [2]. Alongside immune cells, vascular smooth muscle cells (SMCs) contribute significantly to plaque initiation. By altering extracellular matrix composition, facilitating lipid retention, and adopting foam cell-like phenotypes, SMCs participate directly in lesion development. They also express adhesion molecules that enhance leukocyte recruitment and produce cytokines such as PDGF, TGF- β , IFN γ , and MCP-1, thereby amplifying local inflammation. Although traditionally associated with fibrous cap formation in advanced lesions, recent gene-targeting studies underscore their pivotal role in the earliest phases of plaque progression [3].

Toll-like receptor 4 (TLR4) further integrates inflammatory signalling into atherogenesis. Beyond recognizing microbial ligands, TLR4 responds to endogenous molecules released during vascular injury, thereby sustaining chronic inflammation. Evidence from TLR4-deficient mouse models and human polymorphism studies highlights its importance in both the initiation and progression of atherosclerotic disease [4].

2. Disease Progression in Atherosclerosis

The initiation of atherosclerosis is closely linked to dysregulation of lipid metabolism. Under normal conditions, LDL receptor expression is downregulated once intracellular cholesterol requirements are met. However, excessive lipid intake, defective receptor function, or genetic mutations disrupt this control, leading to intimal retention of LDL particles [5,6]. These lipoproteins bind to arterial proteoglycans, becoming prone to oxidative and enzymatic modification, a hallmark of early lesion development [7,8]. Oxidized LDL (oxLDL), generated through vascular NADPH oxidases,

lipoxygenases, or myeloperoxidase activity, promotes endothelial dysfunction by enhancing permeability, leukocyte adhesion, and pro-coagulant activity [7,9]. Endothelial cells upregulate adhesion molecules such as VCAM-1, ICAM-1, and P-selectins, facilitating monocyte recruitment. MCP-1, secreted by endothelial and smooth muscle cells, further drives monocyte migration into the intima. Genetic studies in mice deficient in VCAM-1 or MCP-1 confirm their critical role in early lesion formation [8, 10]. Activated T cells entering via VCAM-1 amplify inflammation through cytokines including IFN- γ and TNF- β , which stimulate macrophages, endothelium, and smooth muscle cells [10].

Once within the intima, monocytes differentiate into macrophages under the influence of macrophage colony-stimulating factor (M-CSF), which upregulates scavenger receptor-A expression and drives uptake of modified LDL to form foam cells [11-13]. Foam cell accumulation creates the fatty streak, the earliest visible atherosclerotic lesion. The local environment is enriched with pro-inflammatory mediators such as cytokines, chemokines, eicosanoids, and platelet-activating factor, sustaining chronic inflammation [7,10,12]. Excessive reactive oxygen species (ROS) production overwhelms antioxidant defenses, exacerbating oxidative stress and arterial injury [7,10,14]. Activated macrophages and lymphocytes release hydrolytic enzymes, growth factors, and inflammatory mediators, perpetuating lesion expansion [8-10]. Importantly, uptake of oxLDL, apoptotic debris, and microbial products through scavenger and Toll-like receptors further activates macrophages. Supporting this, studies in apoE- and TLR-deficient mice revealed reduced lesion formation, highlighting the importance of innate immune signalling in foam cell development [15].

Progression from fatty streaks to advanced atherosclerotic lesions involves migration and proliferation of smooth muscle cells (SMCs) into the intima, accompanied by extracellular matrix (ECM) accumulation and arterial wall remodelling. This remodelling may include compensatory enlargement or calcification, contributing to plaque hardening [5,7]. Activated leukocytes and vascular cells secrete fibrogenic mediators and growth factors, promoting SMC proliferation and synthesis of a dense ECM, which forms the fibrous cap. Platelet-derived growth factor (PDGF), secreted by activated macrophages, is a key driver of SMC migration and proliferation and is consistently overexpressed in human lesions. However, T cell-mediated SMC apoptosis destabilizes plaque structure, further complicating disease progression [8].

In advanced disease, plaque stability declines as activated macrophages secrete proteolytic enzymes, including matrix metalloproteinases (MMPs), which degrade collagen and other ECM components of the fibrous cap [10,15]. Interactions between CD40/CD40L on T cells and macrophages amplify inflammatory signalling, leading to production of tissue factor (TF), MMPs, and pro-inflammatory cytokines [16]. OxLDL, ROS, TNF- α , and IL-1 further enhance MMP expression by foam cells and SMCs, weakening plaque integrity [17]. Excessive MMP activity, together with TF expression and persistent T cell activation, creates a highly unstable lesion prone to rupture.

Rupture exposes thrombogenic plaque contents, generating prothrombotic stimuli that accelerate thrombin formation through TF, von Willebrand factor, and subendothelial collagen, whose expression is upregulated by IL-1, TNF- α , and CD40L. Platelet adhesion and aggregation ensue, amplifying inflammation and driving acute complications such as myocardial infarction [8].

3. Contribution of Immune Cells to Atherosclerosis

Immune cells orchestrate both the progression and modulation of atherosclerosis through complex interactions in the vascular microenvironment. Monocytes infiltrate the intima and differentiate into macrophages, which regulate cholesterol metabolism, drive foam cell formation, and sustain chronic inflammation [18,19]. Dendritic cells, though less abundant, are critical for antigen presentation and T cell activation, thereby linking innate and adaptive immunity [20].

Among T cell subsets, regulatory T cells (Tregs) exert anti-atherogenic effects by suppressing inflammation and stabilizing plaques, whereas Th1 cells, characterized by IFN- γ production, enhance vascular inflammation and lesion development [21]. NKT cells bridge innate and adaptive responses; their activation by lipid antigens promotes cytokine release and cytotoxic activity, contributing to lesion expansion [22,23]. B cells display dual roles: class-switched antibody-producing subsets

exacerbate atherosclerosis, while IgM-producing B1 cells provide protection [24]. Natural killer (NK) cells also demonstrate pro-atherogenic functions through perforin- and granzyme B-mediated cytotoxicity and necrotic core expansion, with experimental models confirming their role in plaque destabilization [25, 26].

The diverse contributions of these immune cells are summarized in **Table 1**, underscoring their multifaceted involvement in atherogenesis.

Table 1. Immunological Aspects of Atherosclerosis

Immune cells	Key role in atherosclerosis
Monocytes/macrophages	Mediate foam cell formation, regulate cholesterol metabolism, sustain chronic inflammation [18,19]
Dendritic cells	Present antigens, activate naïve T cells, induce cytokine release [20]
T cells	Tregs suppress inflammation and stabilize plaques; Th1 cells promote IFN- γ -driven inflammation; NKT cells enhance cytokine release and lesion expansion [21-23]
B cells	Class-switched B cells are pro-atherogenic; IgM-producing B1 cells are protective [24]
NK cells	Promote plaque instability via perforin/granzyme B; NK cell depletion reduces lesions [25,26]

4. Therapeutic Potential of Conventional Drugs in Atherosclerosis Control

(i) Nifedipine: Nifedipine, an L-type calcium channel blocker, exerts anti-atherosclerotic effects through multiple mechanisms. It enhances peroxisome proliferator-activated receptor- γ (PPAR γ) activity in macrophages by inhibiting extracellular signal-regulated kinase 1/2 and PPAR γ 2-Ser112 phosphorylation, thereby promoting lipid efflux pathways [27,28]. Nifedipine also suppresses monocyte chemoattractant protein-1 (MCP-1) and induces ATP-binding cassette transporter A1 (ABCA1) expression in macrophages [29]. In apolipoprotein E-deficient mice, treatment reduced lesion size and MCP-1 expression while increasing ABCA1 expression [30]. Clinical studies further demonstrate that nifedipine restores endothelial function, attenuates vascular inflammation, and decreases coronary events, collectively slowing atherosclerotic progression [31].

(ii) Ramipril: Ramipril, particularly in combination with rosuvastatin, has been shown to reduce intima-media thickness (IMT) and plaque size more effectively than statin monotherapy [32]. Additionally, it lowers circulating high-sensitivity C-reactive protein (hs-CRP) levels, suggesting an anti-inflammatory role that may reduce cardiovascular risk [33].

(iii) Perindopril: Perindopril improves endothelial function and attenuates plaque progression [34]. In experimental models, low doses reduced atherosclerotic plaque formation in cholesterol-fed rabbits [35]. It also enhanced collagen and non-collagen synthesis by smooth muscle cells, limited lipoprotein binding, and mitigated lesion development [36]. Clinically, perindopril has been associated with improved blood pressure profiles and favourable outcomes in patients with hypertension and coronary atherosclerosis undergoing revascularization [37].

5. Therapeutic Potential of Natural Products in Atherosclerosis Control

(i) Flaxseed-Derived Compounds: Flaxseed is rich in α -linolenic acid and lignans, particularly secoisolariciresinol diglucoside (SDG) and flax lignan complex (FLC). SDG levels range between 0.6–1.8 g/100 g of seed, while FLC typically contains 34–38% SDG, 15–21% cinnamic acid glucoside, and 9.6–11% hydroxymethyl glutaric acid [38,39].

SDG exhibits both anti-hyperlipidemic and anti-oxidative effects, contributing to the attenuation of atherosclerosis. In hypercholesterolemic rabbit models, SDG reduced lesion progression by 24% after 2 months and by 45% after 4 months of supplementation, with extended treatment achieving 17.5% lesion regression [40,41]. The benefits were linked to lowered oxidative stress rather than lipid reduction, as cholesterol-fed animals switched to normal diet paradoxically developed accelerated

atherosclerosis. These findings indicate that SDG primarily slows disease progression and, with prolonged use, promotes partial regression through antioxidant mechanisms.

FLC supplementation slowed lesion progression by approximately 31–32% in hypercholesterolemic animal models, an effect accompanied by reduced oxidative stress markers [42,43]. However, it did not induce significant regression of established lesions. Mechanistic studies suggest that the protective role of FLC may involve antioxidant properties, lipid-lowering effects, guanylate cyclase stimulation, nitric oxide donation, and reductions in vascular cholesterol and smooth muscle cell accumulation [44,45].

(ii) *Sphaeranthus indicus*: *Sphaeranthus indicus* (Asteraceae), a traditional Ayurvedic herb, contains diverse bioactive compounds including sesquiterpene lactones such as 7-hydroxyfrullanolide (7-HF). Extracts demonstrate anti-inflammatory and anti-hyperlipidemic properties relevant to atherosclerosis [46].

- **Anti-inflammatory effects.** Methanolic extracts and 7-HF suppress pro-inflammatory cytokine production and inhibit adhesion molecule expression (VCAM-1, ICAM-1, E-selectin) via NF- κ B pathway modulation. In vivo, extracts reduced aortic lesion size in hyperlipidemic mice and hamsters without altering lipid profiles, suggesting an inflammation-driven mechanism [47].
- **Antihyperlipidemic activity.** In rats fed an atherogenic diet, administration of *S. indicus* extract (500 mg/kg/day) reduced total cholesterol, LDL-c, triglycerides, and body weight while increasing HDL-c. The extract improved atherogenic index and lipid ratios, possibly through enhanced lecithin-cholesterol acyltransferase (LCAT) and lipoprotein lipase activity [48].

(iii) Flavonoids: Flavonoids, plant-derived polyphenols, exhibit antioxidant, anti-inflammatory, and endothelial-protective properties that collectively counteract atherosclerotic processes [49,50].

(iii.a) Quercetin: Quercetin exerts anti-atherogenic effects through activation of SIRT1 and AMPK pathways, leading to reduced oxidative stress, inflammation, and endothelial dysfunction [51,52]. It inhibits dendritic cell activation, attenuates vascular senescence, and decreases plaque inflammation in animal models [53]. Supplementation reduces aortic lesions, modulates lipid metabolism, and prevents acute aortic syndromes in hypercholesterolemic animals [54,55].

(iii.b) Anthocyanins: Anthocyanins enhance antioxidant defences, activate Nrf2-regulated genes, and reduce inflammatory signalling [56,57]. Protocatechuic acid, a major metabolite, inhibits monocyte adhesion via NF- κ B suppression [58]. Animal studies demonstrate improved HDL function, reduced aortic cholesterol, and protection against hypercholesterolemia-induced oxidative stress [59–61]. Effects appear source-dependent, with some reports indicating variable impact on lipid profiles [62,63].

(iii.c) Biochanin A: Biochanin A (BCA), an isoflavone, improves lipid profiles by elevating HDL-c and lowering LDL-c and total cholesterol, while suppressing pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6) [64,65]. In apoE^{-/-} mice, BCA reduced lesion size, improved reverse cholesterol transport, and inhibited foam cell formation by decreasing intracellular cholesterol accumulation [66].

(iii.d) Baicalin: Baicalin, isolated from *Scutellaria baicalensis*, exhibits antioxidant, immunomodulatory, and lipid-regulating activities. It inhibits foam cell formation, suppresses TLR4 and iNOS expression, and promotes anti-inflammatory signalling [67,68]. Network pharmacology and experimental studies identified NOX4 as a key target mediating its antioxidative effects, suggesting novel mechanisms for baicalin in atherosclerosis therapy.

Table 2. Clinical trials involving natural antioxidant compounds

Antioxidant	Study Design	Results	Conclusion and Reference
Vitamin E	• A cohort of 87,245 female nurses • Without prior cancer or cardiovascular disease	• 552 severe CAD cases reported. • Women with the highest vitamin E intake showed	• Vitamin E supplementation may lower CAD risk in women aged 34–59 [69].

		a relative risk (RR) of 0.66. • Short-term supplementation showed little effect, while >2 years of supplementation reduced risk (RR = 0.59).	
Quercetin	• 93 overweight or obese subjects. • Received either 150 mg/day quercetin or placebo for 6 weeks.	• Quercetin reduced SBP by 2.6 mmHg and decreased serum HDL-C levels. • Ratios of total cholesterol, TAG/HDL-C, and LDL/HDL-C remained unchanged. • Plasma oxidized LDL decreased. • CRP and TNF-α unaffected.	• Quercetin may help reduce SBP and oxidized LDL, indicating a protective role in CVD [70].
EGCG	• 35 age and sex matched obese patients with metabolic syndrome • Green tea (4 cups/day), control (4 cups water/day), or green tea extract (2 capsules + 4 cups water/day) for 8 weeks. • EGCG doses were similar across tea and extract groups.	• Both green tea and extract groups showed significant weight reduction. • Green tea also reduced LDL-C and LDL/HDL ratio • Significantly lowered lipid peroxidation markers (HNE and MDA).	• Green tea reduces body weight and lipid peroxidation • Suggests a beneficial role in improving metabolic syndrome [71].
Resveratrol	• 66 patients with metabolic syndrome. • Received 150 mg/ day resveratrol, 1,000 mg/day resveratrol, or placebo for 16 weeks.	• No reduction in the plasma levels of soluble urokinase plasminogen activator receptor, hs-CRP, or IL-6. • No change in the expression of inflammatory genes in fat and muscle tissues. • No beneficial effect on lipid or glucose metabolism. • Up-regulated the levels of total cholesterol, LDL C and fructosamine.	• Resveratrol had no beneficial effect on blood glucose homeostasis, inflammatory state, blood pressure or liver lipid content in patients with MetS. • Resveratrol (high dose) up-regulated the levels of total cholesterol, LDL-C and fructosamine [72]
Probucol	• 303 patients with hypercholesterolemia were assigned to receive placebo or probucol combined with dietary	• Probucol treated patients reduced their total cholesterol by 15% and HDL-C by 35%.	• Probucol provides obvious protection against Cu²⁺ catalyzed LDL oxidation.

	recommendations and cholestyramine for 3 years	• The LDL was more resistant to the Cu²⁺ -induced oxidation. • Probucol has no significant effect on the progression and regression of femoral atherosclerosis.	• Probucol do not affect the development of femoral atherosclerosis [73].
lycopene	• 175 Healthy male subjects recruited. • Received supplements of lycopene (15 mg), lutein (15 mg), β carotene (15 mg), or placebo every day for 3 months.	• Supplementation of β-carotene, lycopene, and lutein resulted in an obvious increase in plasma and LDL of these carotenoids. • The levels of other carotenoids in plasma or LDL did not change. • The supplement failed to enhance LDL antioxidant capacity or change the ratio polyunsaturated/ of saturated fatty acids. LDL	• No beneficial or adverse effects of supplementation of β carotene, lycopene or lutein, on oxidative stress observed biomarkers were observed [74].

Table 2. Describes the clinical research design, number of cases, trial results, and conclusions of research on some of the natural products.

Abbreviations: CAD: Coronary artery disease; CVD: Cardiovascular disease; CRP: C-reactive protein; EGCG: Epigallocatechin-3-gallate; HDL-C: High density cholesterol; HNE: Hydroxynonenals; hs-CRP: High-sensitivity C-reactive protein; LDL-C: Low density cholesterol; MDA: Malondialdehyde; MetS: Metabolic syndrome; SBP: Systolic blood pressure; TAG: Triacylglyceride;

6. Soluble Ninjurin-1 as a Potential Anti-Inflammatory Agent in Atherosclerosis

Ninjurin-1 (Ninj1), also known as nerve injury-induced protein 1, has recently been identified as a substrate of matrix metalloproteinase-9 (MMP9) in plaque macrophages. Elevated levels of its soluble form (sNinj1) have been detected in the serum of patients with coronary artery disease. Jeon et al. (2020) [75] investigated the role of Ninj1 in atherosclerosis and reported that Ninj1 cleavage by MMP9 releases sNinj1, which exhibits anti-inflammatory properties. Within atherosclerotic lesions, Ninj1 expression was predominantly localized to alternatively activated macrophages (AAMs), a subset with anti-inflammatory activity.

Their findings indicated that Ninj1 plays a crucial role in maintaining immune balance by suppressing arterial inflammation. Deletion of Ninj1 aggravated inflammatory responses and accelerated atherosclerosis in mouse models, whereas administration of sNinj1 or synthetic peptides mimicking its function reduced inflammation and improved disease outcomes. Mechanistic studies revealed that Ninj1 inhibits pro-inflammatory pathways such as MAPK while simultaneously enhancing anti-inflammatory signalling through PI3K/Akt. Sustained treatment with sNinj1 analogues consistently attenuated inflammation and disease progression without adverse effects. Collectively, these observations highlight the therapeutic potential of targeting Ninj1 processing or mimicking its soluble form as a novel strategy to manage atherosclerosis.

7. Canakinumab: Canakinumab, a fully human monoclonal antibody targeting interleukin-1 β (IL-1 β), has been evaluated for its role in reducing inflammation-driven cardiovascular risk. The

Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) (NCT01327846) is a randomized, double-blind, placebo-controlled, event-driven Phase III study designed to evaluate the efficacy, safety and tolerability of quarterly subcutaneous injections of ACZ885 (also known as canakinumab) in combination with standard of care in the prevention of recurrent cardiovascular (CV) events. Results from the CANTOS trial demonstrated a significant reduction in cardiovascular events among patients with a prior history of myocardial infarction, independent of changes in lipid levels or blood pressure [76,77]. The drug functions by binding specifically to IL-1 β , forming an antigen–antibody complex that prevents IL-1 β from interacting with its receptor IL-1R1, thereby blocking downstream IL-1 signalling. This selectivity minimizes interference with other IL-1 family cytokines, potentially lowering adverse effects such as infection risk. Structural modelling studies using Protein Data Bank (PDB) data confirmed that the Fab fragment of canakinumab overlapped with the D1 domain of IL-1R1, effectively blocking IL-1 β from receptor engagement [78].

Further investigations assessed canakinumab's effect on superficial femoral artery (SFA) plaque burden in patients with peripheral artery disease (PAD) over a 12-month period using high-resolution 3.0T MRI. Although no significant changes in SFA plaque size were noted between treatment and placebo groups, exploratory endpoints revealed early improvements in both maximum and pain-free walking distances among canakinumab-treated patients. This effect may reflect enhanced skeletal muscle perfusion or improved endothelial function, independent of plaque regression. Additionally, treatment significantly reduced circulating interleukin-6 (IL-6), reinforcing its systemic anti-inflammatory action. Interestingly, the differential impact on pain-free versus maximum walking distance suggests possible modulation of pain signalling, potentially by reducing ischemia-induced lactate accumulation. In line with CANTOS, the study highlighted that patients with elevated baseline high-sensitivity C-reactive protein represented a high-inflammatory burden population that could particularly benefit from IL-1 β inhibition.

8. Conclusion

Atherosclerosis is a multifactorial disorder and continues to be a major global cause of death due to its association with cardiovascular events such as coronary artery disease, myocardial infarction, and stroke. Its pathogenesis involves a complex interaction of lipid deposition, immune-inflammatory mechanisms, and diverse risk factors, highlighting the need for multidimensional therapeutic strategies. This review emphasized the influence of both classical risk factors—including elevated LDL cholesterol, hypertension, and smoking—and non-traditional contributors such as poor sleep quality, sedentary lifestyle, and environmental stress.

The therapeutic landscape is shifting toward a combination of conventional drugs and natural product-based interventions. Plant-derived compounds like secoisolariciresinol diglucoside (SDG) and flaxseed lignans (FLC) have shown potential in lowering lipid levels and attenuating inflammation. Likewise, the anti-inflammatory effects of biologics such as canakinumab, along with medicinal plants like *Sphaeranthus indicus*, provide additional treatment opportunities. Flavonoids such as quercetin and anthocyanins, as well as novel molecular targets like Ninjurin-1 (NINJ1), further expand therapeutic possibilities by modulating oxidative stress and immune responses.

Established pharmacological treatments, including antihypertensive drugs such as nifedipine, ramipril, and perindopril, remain central to reducing cardiovascular risk. However, combining these with natural product-based therapies may yield synergistic effects, improving both efficacy and patient outcomes.

Overall, this review highlights the importance of adopting a holistic approach to atherosclerosis management, taking into account its multifactorial nature and the need for tailored treatment strategies. Future investigations should continue to unravel the molecular mechanisms driving atherosclerosis and evaluate the therapeutic promise of both conventional and novel agents. By broadening our understanding and expanding available interventions, we can advance the fight against atherosclerosis and enhance cardiovascular health on a global scale.

Acknowledgements

The authors are grateful to University of Lucknow, Lucknow and Indira Gandhi National Open University, New Delhi for providing basic infrastructure required to carry out the review process.

Consent for publication

Not applicable

Competing interests

All the authors declare that there are no competing interests.

Funding

The work was not funded by any funding agencies.

Authors' contributions

VKS and PS; Collected the primary data and wrote the paper. PKS: Designed the study, analysed the data, and wrote the manuscript. All authors have read and approved the final manuscript.

References

- [1] Herrington, W., Lacey, B., Sherliker, P., Armitage, J., & Lewington, S. (2016). Epidemiology of atherosclerosis and the potential to reduce the global burden of atherothrombotic disease. *Circulation research*, 118(4), 535-546.
- [2] Kawai, K., Finn, A. V., & Virmani, R. (2024). Subclinical Atherosclerosis: Part 1: What is it? Can it Be Defined at the Histological Level? *Arteriosclerosis, Thrombosis, and Vascular Biology*, 44(1), 12-23.
- [3] Doran, A. C., Meller, N., & McNamara, C. A. (2008). Role of smooth muscle cells in the initiation and early progression of atherosclerosis. *Arteriosclerosis, thrombosis, and vascular biology*, 28(5), 812-819.
- [4] Pasterkamp, G., Van Keulen, J. K., & De Kleijn, D. P. V. (2004). Role of Toll-like receptor 4 in the initiation and progression of atherosclerotic disease. *European journal of clinical investigation*, 34(5), 328-334.
- [5] Li, H., Cybulsky, M. I., Gimbrone Jr, M. A., & Libby, P. (1993). An atherogenic diet rapidly induces VCAM-1, a cytokine-regulatable mononuclear leukocyte adhesion molecule, in rabbit aortic endothelium. *Arteriosclerosis and thrombosis: a journal of vascular biology*, 13(2), 197-204.
- [6] Cybulsky, M. I., Iiyama, K., Li, H., Zhu, S., Chen, M., Iiyama, M., ... & Milstone, D. S. (2001). A major role for VCAM-1, but not ICAM-1, in early atherosclerosis. *The Journal of clinical investigation*, 107(10), 1255-1262.
- [7] Johnson, R. C., Chapman, S. M., Dong, Z. M., Ordovas, J. M., Mayadas, T. N., Herz, J., ... & Wagner, D. D. (1997). Absence of P-selectin delays fatty streak formation in mice. *The Journal of clinical investigation*, 99(5), 1037-1043.
- [8] Dong, Z. M., Chapman, S. M., Brown, A. A., Frenette, P. S., Hynes, R. O., & Wagner, D. D. (1998). The combined role of P-and E-selectins in atherosclerosis. *The Journal of clinical investigation*, 102(1), 145-152.
- [9] Collins, T., & Cybulsky, M. I. (2001). NF- κ B: pivotal mediator or innocent bystander in atherogenesis?. *The Journal of clinical investigation*, 107(3), 255-264.
- [10] Topper, J. N., & Gimbrone Jr, M. A. (1999). Blood flow and vascular gene expression: fluid shear stress as a modulator of endothelial phenotype. *Molecular medicine today*, 5(1), 40-46.
- [11] Alexander, R. W. (1995). Hypertension and the pathogenesis of atherosclerosis: oxidative stress and the mediation of arterial inflammatory response: a new perspective. *Hypertension*, 25(2), 155-161.
- [12] Sairanen, T. (2001). Mediators of inflammation in cerebral ischemia: roles of cytokine and cyclooxygenase-2 activation: Expression of interleukin-1beta, tumor necrosis factor-alpha, their

- receptors, and cyclooxygenase-2 in experimental and clinical brain infarction (Doctoral dissertation, Helsingin yliopisto)
- [13] Bobková, D., & Poledne, R. (2003). Lipid metabolism in atherogenesis. *Ceskoslovenska Fysiologie*, 52(1), 34-41.
- [14] Martindale, J. L., & Holbrook, N. J. (2002). Cellular response to oxidative stress: signaling for suicide and survival. *Journal of cellular physiology*, 192(1), 1-15.
- [15] Michel, N. A., Zirlik, A., & Wolf, D. (2017). CD40L and its receptors in atherothrombosis—an update. *Frontiers in cardiovascular medicine*, 4, 40.
- [16] Szmítko, P. E., Wang, C. H., Weisel, R. D., Jeffries, G. A., Anderson, T. J., & Verma, S. (2003). Biomarkers of vascular disease linking inflammation to endothelial activation: Part II. *Circulation*, 108(17), 2041-2048.
- [17] Galis, Z. S., & Khatri, J. J. (2002). Matrix metalloproteinases in vascular remodeling and atherogenesis: the good, the bad, and the ugly. *Circulation research*, 90(3), 251-262.
- [18] Theofilis, P., Oikonomou, E., Tsioufis, K., & Tousoulis, D. (2023). The role of macrophages in atherosclerosis: pathophysiologic mechanisms and treatment considerations. *International Journal of Molecular Sciences*, 24(11), 9568.
- [19] Guo Z, Wang L, Liu H, Xie Y. Innate Immune Memory in Monocytes and Macrophages: The Potential Therapeutic Strategies for Atherosclerosis. *Cells*. 2022; 11(24):4072.
- [20] Zhao, Y., Zhang, J., Zhang, W., & Xu, Y. (2021). A myriad of roles of dendritic cells in atherosclerosis. *Clinical & Experimental Immunology*, 206(1), 12-27.
- [21] Chen J, Xiang X, Nie L, Guo X, Zhang F, Wen C, Xia Y, Mao L. (2023). The emerging role of Th1 cells in atherosclerosis and its implications for therapy. *Front Immunol*. 13:1079668. doi: 10.3389/fimmu.2022.1079668
- [22] Samson S., Mundkur L., Kakkar V.V. (2012). Immune Response to Lipoproteins in Atherosclerosis. *Cholesterol* 571846, 12 pages, 2012. <https://doi.org/10.1155/2012/571846>
- [23] Chakrabarti R, Duddu S, Tiwari A, Naidu KT, Sharma P, Chakravorty N, Shukla PC (2023). Natural Killer T cells and the invariant subset promote atherosclerosis: A meta-analysis. *Life Sci*. 321:121620. doi: 10.1016/j.lfs.2023.121620.
- [24] Ebrahimian T., Dierick F., Ta V. et al. (2023). B cell-specific knockout of AID protects against atherosclerosis. *Sci Rep* 13, 8723. <https://doi.org/10.1038/s41598-023-35980-1>
- [25] Selathurai, A., Deswaerte, V., Kanellakis, P., Tipping, P., Toh, B. H., Bobik, A., & Kyaw, T. (2014). Natural killer (NK) cells augment atherosclerosis by cytotoxic-dependent mechanisms. *Cardiovascular research*, 102(1), 128-137.
- [26] Cavallari, M., Resink, T. J., & De Libero, G. (2011). NK/NKT Cells and Atherosclerosis. In *Inflammation and Atherosclerosis* (pp. 305-330). Vienna: Springer Vienna.
- [27] Ishii, N., Matsumura, T., Kinoshita, H., Fukuda, K., Motoshima, H., Senokuchi, T., ... & Araki, E. (2010). Nifedipine induces peroxisome proliferator-activated receptor- γ activation in macrophages and suppresses the progression of atherosclerosis in apolipoprotein E-deficient mice. *Arteriosclerosis, thrombosis, and vascular biology*, 30(8), 1598-1605.
- [28] Verhaar, M. C., Honing, M. L., van Dam, T., Zwart, M., Koomans, H. A., Kastelein, J. J., & Rabelink, T. J. (1999). Nifedipine improves endothelial function in hypercholesterolemia, independently of an effect on blood pressure or plasma lipids. *Cardiovascular research*, 42(3), 752-760.
- [29] Ueng, K. C., Lin, M. C., Chan, K. C., & Lin, C. S. (2007). Nifedipine gastrointestinal therapeutic system: an overview of its antiatherosclerotic effects. *Expert Opinion on Drug Metabolism & Toxicology*, 3(5), 769-780.
- [30] Yamagishi, S. I., Nakamura, K., Takenaka, K., Matsui, T., & Inoue, H. (2006). Pleiotropic effects of nifedipine on atherosclerosis. *Current pharmaceutical design*, 12(12), 1543-1547.
- [31] Yamagishi, S., & Takeuchi, M. (2005). Atheroprotective properties of nifedipine. *International journal of tissue reactions*, 27(2), 63-67.

- [32] Schlimmer, N., Kratz, M., Böhm, M., & Baumhäkel, M. (2011). Telmisartan, ramipril and their combination improve endothelial function in different tissues in a murine model of cholesterol-induced atherosclerosis. *British journal of pharmacology*, 163(4), 80
- [33] Raj, K., Ravinder, G., Simmi, A., Kamlesh, K., & Gansham, M. (2014). Comparative Study of Rosuvastatin as Monotherapy versus Rosuvastatin with Ramipril in Dyslipidemia and Their Effects on Atherosclerosis. *American Journal of Medical Sciences*, 2(3), 58-63
- [34] Osipova, O. A., Kurbakov, N. N., Ovsyannikov, A. G., & Vlasenko, M. A. (2016). Comparative evaluation of the antihypertensive effect of perindopril and losartan potassium in patients with arterial hypertension and stenotic coronary atherosclerosis before revascularization: an open randomized comparative study. *Rational Pharmacotherapy in Cardiology*, 7(3), 300-305.
- [35] Fox, K. (2008). Benefits of perindopril all along the cardiovascular continuum: the level of evidence. *European heart journal supplements*, 10(suppl_G), G4-G12.
- [36] Campbell, J. H., Fennessy, P., & Campbell, G. R. (1992). Effect of Perindopril on the development of atherosclerosis in the cholesterol-fed rabbit. *Clinical and Experimental Pharmacology and Physiology*, 19(S19), 13-17.
- [37] Fennessy, P. A., Campbell, J. H., & Campbell, G. R. (1994). Perindopril inhibits both the development of atherosclerosis in the cholesterol-fed rabbit and lipoprotein binding to smooth muscle cells in culture. *Atherosclerosis*, 106(1), 29-41.
- [38] Prasad, K., Mantha, S. V., Muir, A. D., & Westcott, N. D. (1998). Reduction of hypercholesterolemic atherosclerosis by CDC-flaxseed with very low alpha-linolenic acid. *Atherosclerosis*, 136(2), 367-375.
- [39] Prasad, K. (2005). Hypocholesterolemic and antiatherosclerotic effect of flax lignan complex isolated from flaxseed. *Atherosclerosis*, 179(2), 269-275.
- [40] Prasad, K. (2000). Antioxidant activity of secoisolariciresinoldiglucoside-derived metabolites, secoisolariciresinol, enterodiol, and enterolactone. *International journal of angiology*, 9(04), 220-225.
- [41] Prasad, K. (2008). Regression of hypercholesterolemic atherosclerosis in rabbits by secoisolariciresinoldiglucoside isolated from flaxseed. *Atherosclerosis*, 197(1), 34-42.
- [42] Zanzwar, A. A., Hegde, M. V., & Bodhankar, S. L. (2014). Flax lignan in the prevention of atherosclerotic cardiovascular diseases. In *Polyphenols in human health and disease* (pp. 915-921). Academic Press.
- [43] Prasad, K. (2007). A study on regression of hypercholesterolemic atherosclerosis in rabbits by flax lignan complex. *Journal of cardiovascular pharmacology and therapeutics*, 12(4), 304-313.
- [44] Schuler, D., Sansone, R., Heiss, C., & Kelm, M. (2013). Is there a Role for Antioxidants in the Treatment of Stable Angina? *Current pharmaceutical design*, 19(9), 1601-1615.
- [45] Cooke, J. P., Singer, A. H., Tsao, P., Zera, P., Rowan, R. A., & Billingham, M. E. (1992). Antiatherogenic effects of L-arginine in the hypercholesterolemic rabbit. *The Journal of clinical investigation*, 90(3), 1168-1172.
- [46] Singh S, Semwal BC, Kr Upadhaya P. (2019). Pharmacognostic study of *Sphaeranthus indicus* Linn. A Review. *Pharmacog J*. 11(6):1376-85.
- [47] Srivastava, R. A. K., Mistry, S., & Sharma, S. (2015). A novel anti-inflammatory natural product from *Sphaeranthus indicus* inhibits expression of VCAM1 and ICAM1, and slows atherosclerosis progression independent of lipid changes. *Nutrition & metabolism*, 12, 1-16.
- [48] Pande, V. V., & Dubey, S. (2009). Antihyperlipidemic activity of *Sphaeranthus indicus* on atherogenic diet induced hyperlipidemia in rats. *International Journal of Green Pharmacy (IJGP)*, 3(2).
- [49] Jiang YH, Jiang LY, Wang YC, Ma DF, Li X. (2020). Quercetin Attenuates Atherosclerosis via Modulating Oxidized LDL-Induced Endothelial Cellular Senescence. *Front Pharmacol*. 11:512. doi: 10.3389/fphar.2020.00512.
- [50] Farnaz Ebrahimi, Mohammad Mahdi Ghazimoradi, Ghizal Fatima, Roodabeh Bahramsoltani (2023). Citrus flavonoids and adhesion molecules: Potential role in the management of atherosclerosis. *Heliyon* 9 (11): e21849 <https://doi.org/10.1016/j.heliyon.2023.e21849>.

- [51] Hung, C., Chan, S., Chu, P., & Tsai, K. (2015). Quercetin is a potent anti-atherosclerotic compound by activation of SIRT1 signaling under oxLDL stimulation.. *Molecular nutrition & food research*, 59 10, 1905-17 .
- [52] Lu, X. L., Zhao, C. H., Yao, X. L., & Zhang, H. (2017). Quercetin attenuates high fructose feeding-induced atherosclerosis by suppressing inflammation and apoptosis via ROS-regulated PI3K/AKT signaling pathway. *Biomedicine & Pharmacotherapy*, 85, 658-671.
- [53] Lin, W., Wang, W., Wang, D., & Ling, W. (2017). Quercetin protects against atherosclerosis by inhibiting dendritic cell activation.. *Molecular nutrition & food research*, 61 9.
- [54] Bhaskar S, Kumar KS, Krishnan K, Antony H. (2013). Quercetin alleviates hypercholesterolemic diet induced inflammation during progression and regression of atherosclerosis in rabbits. *Nutrition* 29(1):219-29. doi: 10.1016/j.nut.2012.01.019.
- [55] Kondo M, Izawa-Ishizawa Y, Goda M, Hosooka M, Kagimoto Y, Saito N, Matsuoka R, Zamami Y, Chuma M, Yagi K, Takechi K, Tsuneyama K, Ishizawa K. (2020). Preventive Effects of Quercetin against the Onset of Atherosclerosis-Related Acute Aortic Syndromes in Mice. *Int J Mol Sci*. 21(19):7226. doi: 10.3390/ijms21197226.
- [56] Garcia, C., & Blesso, C. N. (2021). Antioxidant properties of anthocyanins and their mechanism of action in atherosclerosis. *Free Radical Biology and Medicine*, 172, 152-166.
- [57] Aboonabi, A., & Singh, I. (2015). Chemopreventive role of anthocyanins in atherosclerosis via activation of Nrf2–ARE as an indicator and modulator of redox. *Biomedicine & Pharmacotherapy*, 72, 30-36.
- [58] Wang, D., Wei, X., Yan, X., Jin, T., & Ling, W. (2010). Protocatechuic acid, a metabolite of anthocyanins, inhibits monocyte adhesion and reduces atherosclerosis in apolipoprotein E-deficient mice.. *Journal of agricultural and food chemistry*, 58 24, 12722
- [59] Luo, Y., Fang, J. L., Yuan, K., Jin, S. H., & Guo, Y. (2019). Ameliorative effect of purified anthocyanin from *Lycium ruthenicum* on atherosclerosis in rats through synergistic modulation of the gut microbiota and NF-κB/SREBP-2 pathways. *Journal of Functional Foods*, 59, 223-233.
- [60] Millar CL, Norris GH, Jiang C, Kry J, Vitols A, Garcia C, Park YK, Lee JY, Blesso CN. (2018). Long-Term Supplementation of Black Elderberries Promotes Hyperlipidemia, but Reduces Liver Inflammation and Improves HDL Function and Atherosclerotic Plaque Stability in Apolipoprotein E-Knockout Mice. *Mol Nutr Food Res*. 62(23):e1800404. doi: 10.1002/mnfr.201800404.
- [61] Sankhari JM, Thounaojam MC, Jadeja RN, Devkar RV, Ramachandran AV (2012). Anthocyanin-rich red cabbage (*Brassica oleracea* L.) extract attenuates cardiac and hepatic oxidative stress in rats fed an atherogenic diet. *J Sci Food Agric* 92(8):1688-1693.
- [62] Reis JF, Monteiro VV, de Souza Gomes R, do Carmo MM, da Costa GV, Ribera PC, Monteiro MC (2016). Action mechanism and cardiovascular effect of anthocyanins: a systematic review of animal and human studies. *J Transl Med*. 14(1):315. doi: 10.1186/s12967-016-1076-5.
- [63] Shen J, Li X, Zhang X, Li Z, Abulaiti G, Liu Y, Yao J, Zhang P (2022). Effects of Xinjiang wild cherry plum (*Prunus divaricata* Ledeb) anthocyanin-rich extract on the plasma metabolome of atherosclerotic apoE-deficient mice fed a high-fat diet. *Front Nutr* 9:923699. doi: 10.3389/fnut.2022.923699.
- [64] Sethumathi, P. P., Uddandrao, V. S., Chandrasekaran, P., Sengottuvelu, S., Tamilmani, P., & Ponmurugan, P. (2023). Biochanin-A Protects Rats from Diabetes-associated Cardiorenal Damage by Attenuating Oxidative Stress through Activation of Nrf-2/HO-1 Pathway. *Biosciences Biotechnology Research Asia*, 20(2), 499-509.
- [65] Yu, X. H., Chen, J. J., Deng, W. Y., Xu, X. D., Liu, Q. X., Shi, M. W., & Ren, K. (2020). Biochanin A mitigates atherosclerosis by inhibiting lipid accumulation and inflammatory response. *Oxidative Medicine and Cellular Longevity*, 2020, 1-15.
- [66] Galindo CL, Khan S, Zhang X, Yeh YS, Liu Z, Razani B (2023). Lipid-laden foam cells in the pathology of atherosclerosis: shedding light on new therapeutic targets. *Expert Opin Ther Targets* 27(12):1231-1245.

- [67] Li M, Ren C (2022). Exploring the protective mechanism of baicalin in treatment of atherosclerosis using endothelial cells deregulation model and network pharmacology. *BMC Complement Med Ther* 22(1):257. doi: 10.1186/s12906-022-03738-3
- [68] Wang Li, Huang Shenyi, Liang Xiaolun, Zhou Junliang, Han Yifan, He Jiangshan, Xu Danping (2024). Immuno-modulatory role of baicalin in atherosclerosis prevention and treatment: current scenario and future directions. *Frontiers in Immunology* 15 – 2024. doi: 10.3389/fimmu.2024.1377470
- [69] Stampfer, M. J., Hennekens, C. H., Manson, J. E., Colditz, G. A., Rosner, B., & Willett, W. C. (1993). Vitamin E consumption and the risk of coronary disease in women. *The New England Journal of Medicine*, 328(20), 1444–1449.
- [70] Egert, S., Bosy-Westphal, A., Seiberl, J., Kürbitz, C., Settler, U., Plachta- Danielzik, S., Müller, M. J. (2009). Quercetin reduces systolic blood pressure and plasma oxidised low-density lipoprotein concentrations in overweight subjects with a high-cardiovascular disease risk phenotype: A double-blinded, placebo-controlled cross-over study. *The British Journal of Nutrition*, 102(7), 1065–1074.
- [71] Basu, A., Sanchez, K., Leyva, M. J., Wu, M., Betts, N. M., Aston, C. E., & Lyons, T. J. (2010). Green tea supplementation affects body weight, lipids, and lipid peroxidation in obese subjects with metabolic syndrome. *Journal of the American College of Nutrition*, 29(1), 31–40.
- [72] Kjær, T. N., Ornstrup, M. J., Poulsen, M. M., Stødkilde-Jørgensen, H., Jessen, N., Jørgensen, J. O. L., ... Pedersen, S. B. (2017). No beneficial effects of resveratrol on the metabolic syndrome: A randomized placebo-controlled clinical trial. *Journal of Clinical Endocrinology and Metabolism*, 102(5), 1642–1651
- [73] Regnström, J., Walldius, G., Nilsson, S., Elinder, L. S., Johansson, J., Mölgaard, J., ... Nilsson, J. (1996). The effect of probucol on low density lipoprotein oxidation and femoral atherosclerosis. *Atherosclerosis*, 125(2), 217–229.
- [74] Hininger, I. A., Meyer-Wenger, A., Moser, U., Wright, A., Southon, S., Thurnham, D., ... Roussel, A. M. (2001). No significant effects of lutein, lycopene or beta-carotene supplementation on biological markers of oxidative stress and LDL oxidizability in healthy adult subjects. *Journal of the American College of Nutrition*, 20(3), 232–238.
- [75] Jeon, S., Kim, T. K., Jeong, S. J., Jung, I. H., Kim, N., Lee, M. N., & Oh, G. T. (2020). Anti-inflammatory actions of soluble Ninjurin-1 ameliorate atherosclerosis. *Circulation*, 142(18), 1736-1751.
- [76] Rothman, A. M., MacFadyen, J., Thuren, T., Webb, A., Harrison, D. G., Guzik, T. J., & Ridker, P. M. (2020). Effects of interleukin-1 β inhibition on blood pressure, incident hypertension, and residual inflammatory risk: a secondary analysis of CANTOS. *Hypertension*, 75(2), 477-482.
- [77] Ridker, P. M. (2018). Anti-inflammatory therapy for atherosclerosis: interpreting divergent results from the CANTOS and CIRT clinical trials. *Journal of internal medicine*, 285(5), 503-509.
- [78] Mai W, Liao Y (2020). Targeting IL-1 β in the Treatment of Atherosclerosis. *Front Immunol*. 11:589654. doi: 10.3389/fimmu.2020.589654