BIOMOLECULES AND THE NATURAL PRODUCTS FOR THE TREATMENT AND MANAGEMENT OF ATHEROSCLEROSIS

Ragunathan Muthusamy, Nivetha Selladurai, Kamale Sakthivel, Madhubala Selladurai, Sona Balamurugan

[1]Department of Pharmacognosy, Swamy Vivekananda College of Pharmacy, Tiruchengode, Namakkal-637205, TamilNadu, India (Affiliated to The Tamil Nadu Dr.M.G.R. Medical University), Chennai

ABSTRACT

The most prevalent kind of cardiovascular disease (CVD) is atherosclerosis, a chronic inflammatory condition marked by oxidative stress, lipid buildup, and progressive thickening of the arterial intima that eventually results in peripheral vascular disorders, coronary artery disease, and stroke. With a disproportionate burden in low- and middle-income nations, cardiovascular disease (CVD) continues to be the world's leading cause of morbidity and mortality, accounting for about one-third of all deaths globally."The atherosclerotic progression originates prenatally, advancing unnoticed over many years before presenting as major cardiovascular incidents such as heart attack or stroke. The main risk factors for plaque development, instability, and thrombosis are elevated low-density lipoprotein (LDL) cholesterol, hypertension, diabetes mellitus, smoking, obesity, and chronic inflammation. Nutraceuticals and bioactive substances produced from plants have received a lot of interest lately as supplementary approaches to the management and prevention of atherosclerosis. *Vitis vinifera* (Resveratrol), *Salvia miltiorrhiza*(Rosmarinic acid), *Panax notoginseng*(Quercetin and NotoginsenosideR1),*Coptis chinensis* (Berberine),*Linum usitatissimum*(Omega-3 Fatty Acids),*Camellia sinensis, Sesamum indicum* (Sesamin and Sesamol),*Curcuma longa* (Curcumin), *Punica granatum* (Ellagic Acid),*Cynara scolymus* (Artichoke),and fermented soybean products containing nattokinase have all shown anti-atherosclerotic effects. All of these results point to the potential benefits of herbal products and nutraceuticals as supplemental methods for lowering the burden of atherosclerosis.

Keywords: Atherosclerosis; Cardiovascular disease; Low-density lipoprotein; Diabetes Mellitus,Hypertension;Heart Attack, Stroke,Nutraceuticals, Herbal medicines

INTRODUCTION

The most prevalent kind of cardiovascular disease (CVD), atherosclerosis or coronary artery disease (CAD), is primarily characterised by cholesterol buildup and inflammation of the large arteries, which may eventually result in its clinical consequences(Björkegren JLM *et al.,* 2022). Cardiovascular disease, which accounts for 44% of the country's mortality and a large portion of its morbidity, poses a major danger to life as well as health. In addition, cardiovascular disease with atherosclerosis is a developing concern because of the increasing number of elderly people. Atherosclerotic cardiovascular disease is a broad process that encompasses the heart, brain, and peripheral arteries (Kannel WB *et al.,* 1998).

In wealthy nations, atherosclerosis has long been a leading cause of death due to hyperlipidemia and lipid oxidation. The Greek word atherosclerosis refers to the buildup of fat and thickening of the intimal layer of arteries. The fibrous cap covers the fatty substance that is found in the plaque's central core. The two components of atherosclerosis are sclerosis (fibrosis layer made up of smooth muscle cells [SMC], leukocytes, and connective tissue) and atherosis (fat build-up accompanied by many macrophages) (Rafieian-Kopaei M *et al*., 2014).

The development of this plaque begins via the accumulation of tiny cholesterol crystals across the intima and the smooth muscle underneath it. Then, the plaques proliferate and produce fibrous tissue thatsurrounds the smooth muscle, leading to in decrease in blood flow. The creation of connective tissue by fibroblasts and calcium accumulation in the lesion eventually result in sclerosis or hardening of the arteries and finally causes an abrupt stoppage of blood flow. A spike in lipid and blood sugar is connected to the growth in oxidative damage, which influences the antioxidant state and lipoprotein levels. Along with obesity, elevated blood pressure, inflammation, and infectious agents are further causes of atherosclerosis (Hadipour E *et al.,* 2023).

Peripheral vascular disease, ischemic heart disease, and stroke are all included in cardiovascular disease (CVD), which is caused by atherosclerosis, a chronic inflammatory

condition that affects medium- and large-sized arteries, which continue to be the biggest issue facing modern medicine and healthcare. In industrialised societies, atherosclerotic illnesses are responsible for over half of all deaths. The formation of atherosclerotic lesions has a protracted asymptomatic period. Atherosclerosis is primarily caused by elevated LDL (low-density lipoprotein) cholesterol, which can be efficiently reduced by medications like statins and PCSK9 (proprotein convertase subtilisin / kexin type 9) inhibitors. The risk of major cardiovascular events is reduced by approximately 50% and LDL cholesterol is significantly lowered by both treatments. (Kobiyama K *et al*., 2018; Orekhov AN *et al*., 2017).

Additional indicators of risk for atherosclerosis and its thrombotic consequences involve hypertension, tobacco use and diabetes mellitus. The growing evidence also suggests to an involvement of the immune system, since rising risk factors encompass inflammation and clonal haematopoiesis (Libby P *et al.,* 2019).

EPIDEMIOLOGY

Cardiovascular disease is commonly regarded as "the disease of the century" since it is the primary cause of disability and early death globally, accounting for almost 50% of all deaths (Luca AC*etal.,* 2023;Burlutskaya Av*etal.,* 2021). According to epidemiological studies conducted up to 2020, CVD killed nearly 17 million individuals globally in 2015, accounting for 31% of all deaths worldwide, and affected 422.7 million people. Due to inadequate access to healthcare facilities, over 75% of CVD-related deaths worldwide occur in low- and middle-income countries. This can delay the identification of the atherosclerotic process until the symptomatic phase, hence increasing premature mortality from CVD(Luca AC*etal.,* 2023).

The atherosclerotic process starts in the womb by increasing carotid intima-media thickness in fetuses and infants, which greatly increases the prevalence and progression of the atherosclerotic process in children and adolescents, according to epidemiological, clinical, and morphological studies (Burlutskaya Av *et al.,* 2021)."Fatty streaks" were found in 29% of aortas in newborns under one year old and in 3.1% of coronary arteries in children between one and nine years old, according to a Japanese study on people ages one month to thirty-nine. There is strong evidence that children and adolescents should be included in primary atherosclerosis prophylactic strategies. The majority of children above the age of three had

aorta fatty streaks, according to epidemiological research conducted in the United States (Hong YM *et al.,* 2010,Tanaka K *et al.,* 1988;Holman RL *et al.,* 1958).

PATHOPHYSIOLOGY AND PATHOGENESIS

The hardening of arteries brought on by the development of plaques made of fatty acids, cholesterol, calcium, fibrin, cellular debris, and waste products in the subendothelium is known as atherosclerosis. Vital organs like the heart, brain, kidneys, pelvis, arms, and lower limbs may experience hypoxia as a result of the various degrees of artery stenosis, which might totally block blood flow. The disease known as thrombosis occurs when plaques become unstable and rupture, causing blood to coagulate at the rupture site and further obstructing downstream veins or arteries (Ajoolabady A *et al.,* 2024) Depending on which arteries are affected, they are known by several names:

- Carotid artery disease involves plaque formation in the neck arteries. It lowers blood flow to the brain.
- Coronary artery disease (CAD) involves plaque buildup in the arteries of the heart.
- Peripheral artery disease (PAD) usually involves plaque formation in the arteries of the legs, but can also occur in the arms or pelvis.
- Renal artery stenosis refers to plaque buildup in the arteries that carry blood to the kidneys.
- Vertebral artery disorders trigger atherosclerosis in the arteries that carry blood to the back of the brain. This part of the brain regulates physiological functions required to keep a person alive.
- Mesenteric artery ischemia refers to plaque buildup in the arteries that supply blood to the intestines.

LDL TRAPPING FOR EARLY LESION FORMATION

Adaptive intimal thickening and intimal xanthoma, or "fatty streak" in the AHA classification, are two nonatherosclerotic intimal lesions that make up the early lesions.A lesion with a lot of foamy macrophages and no external lipid pools is called an intimal xanthoma. Adaptive intimal thickening, which is mostly composed of smooth muscle cells in a matrix rich in proteoglycans, develops in regions of low shear stress and is present from birth. Research

indicates that intimal xanthomas may not always develop into more severe forms of atherosclerosis and may even reverse (Renu Virmani *et al.,* 2025)

One of the primary causes of atherosclerosis is thought to be hypercholesterolemia. Lipids, particularly LDL-C particles, can migrate into the artery wall due to increases in arterial endothelial permeability brought on by elevated plasma cholesterol levels (Bergheanu SC*et al.,* 2017). Superoxide (O2•), hydroxyl radicals (•OH), and other free radicals generated by the surrounding cells, like HClO, can damage low-density lipoproteins (LDLs). Furthermore, the enzymatic activity of phospholipases and lipoxygenases can directly oxidise LDLs. The lack of protective plasma antioxidants, such as tocopherol, ascorbate, urate, apolipoproteins, or serum albumin, facilitates this process. Ox LDL-derived compounds cause macrophages to express inflammatory molecules (Jebari-Benslaiman S *et al.,* 2022)

ENDOTHELIAL CELL ACTIVATION

Endothelial cell activation is significantly influenced by oxidised lipids and cytokines. T cells and monocytes penetrate the vascular intima. Ox-LDL contributes to T cell activation and functions as an antigen for T cells, causing them to release cytokines that activate macrophages and change endothelium and SMC (Rafieian-Kopaei M *et al.,* 2014)

FORMATION OF FATTY STREAK

When EC expresses chemotactic proteins and adhesion molecules, monocytes are drawn to the vessel wall. Macrophages cannot absorb native LDL; instead, it must first undergo oxidation or aggregation. Through scavenger receptors or phagocytosis of aggregated lipoproteins, lesional macrophages can absorb such "modified" intimal lipoproteins, resulting in cholesterol-engorged macrophages or "foam cells." Even though foam cells can use the transporters ABCA1 and ABCG1 to efflux cholesterol, they often experience apoptosis or necrosis, which results in a developing "necrotic core" made up of cholesterol esters, cholesterol crystals, and cell debris that raises the risk of lesion rupture. During the different stages of atherosclerosis, macrophages also experience metabolic changes that may have an impact on their functioning (Björkegren JLM *et al.,* 2022)

DEVELOPMENT OF FIBROUS PLAQUE

A fibro proliferative response mediated by intimal smooth muscle cells joins the immunoinflammatory response as the disease progresses. These cells are in charge of damage repair and healing. The reparative reaction may become so extensive and dominant that lumen is lost, blood flow is decreased, and ischemia develops if the atherogenic stimuli continue for years, as they frequently do (Falk E *et al.,* 2006).

LIPID RICH CORE

When the foam cells die and the lipid remains as a soft, unstable, and relatively inactive necrotic (atheromatous) core within the plaque, the protective function may be overpowered and transformed into a harmful disease-causing pathway. The lipid-rich atheromatous core is completely devoid of supporting collagen, avascular, hypocellular, and soft-like (Falk E *et al.,* 2006).

FORMATION OF ATHEROMA

When surrounding SMC and endothelial cells release tiny peptides like cytokines and growth factors like interleukin 1 (IL-1) and TNF (which promotes cell proliferation), severe damage to vascular tissue results. The fibrous cap in such an instance is formed by the migration of smooth muscle cells and the synthesis of extracellular matrix. Collagen-rich fibre tissues, SMC, macrophages, and T lymphocytes make up the fibrous cap. They all contribute to the formation of mature atherosclerotic plaque, which enlarges the channel and lowers the blood flow in the capillaries (Steinbrecher UP *et al.,* 1984).

NECROSIS

Endothelial cells, macrophages, and smooth muscle cells undergo apoptosis or necrosis as atherosclerosis develops, creating a fibrous cap that is brittle and prone to rupture as well as a destabilising lipid-rich core, while many macrophages appeared to die inside the lesion, leaving regressive plaques (Falk E *et al.,* 2006).

CALCIFICATION

Atherosclerotic plaques frequently develop focal calcification, which gets worse with age (Falk E *et al.,* 2006) this process can arise from microvessels, the medial layer of arteries, the artery intima, or the valve leaflet. The four different types of vascular calcification that can be

recognised clinically are calcification of the aortic valve and medial vascular, atherosclerotic calcification, and vascular calciphylaxis. Intimal calcification has been related to arterial obstruction and atherosclerotic plaque. However, medial calcification, which can lead to diastolic dysfunction and heart failure, is linked to increased pulse wave velocity, systolic hypertension, and vascular stiffness (Manish Lamoria MD*et al.,* 2024).

PLAQUE STABILITY

According to research on human atherosclerosis, repeated cycles of thrombosis and microhaemorrhage may be involved in the development of advanced plaques. Platelet adhesion, thrombosis, and the coagulation cascade are all triggered by plaque rupture, which exposes plaque lipids and tissue factor to blood components. Macrophage-secreted matrix metalloproteinases have been found in areas of plaque rupture and are thought to affect plaque stability by breaking down extracellular matrix proteins. Human atherosclerotic lesions linked to plaque rupture, bleeding, or unstable angina (progressive episodes of transitory heart ischemia leading to transient thrombus development) frequently exhibit neovascularisation. Neovascularisation may be a factor in plaque instability and rupture since angiogenesis is linked to remodelling and protease activation in surrounding tissues(Glass CK *et al.,* 2001).

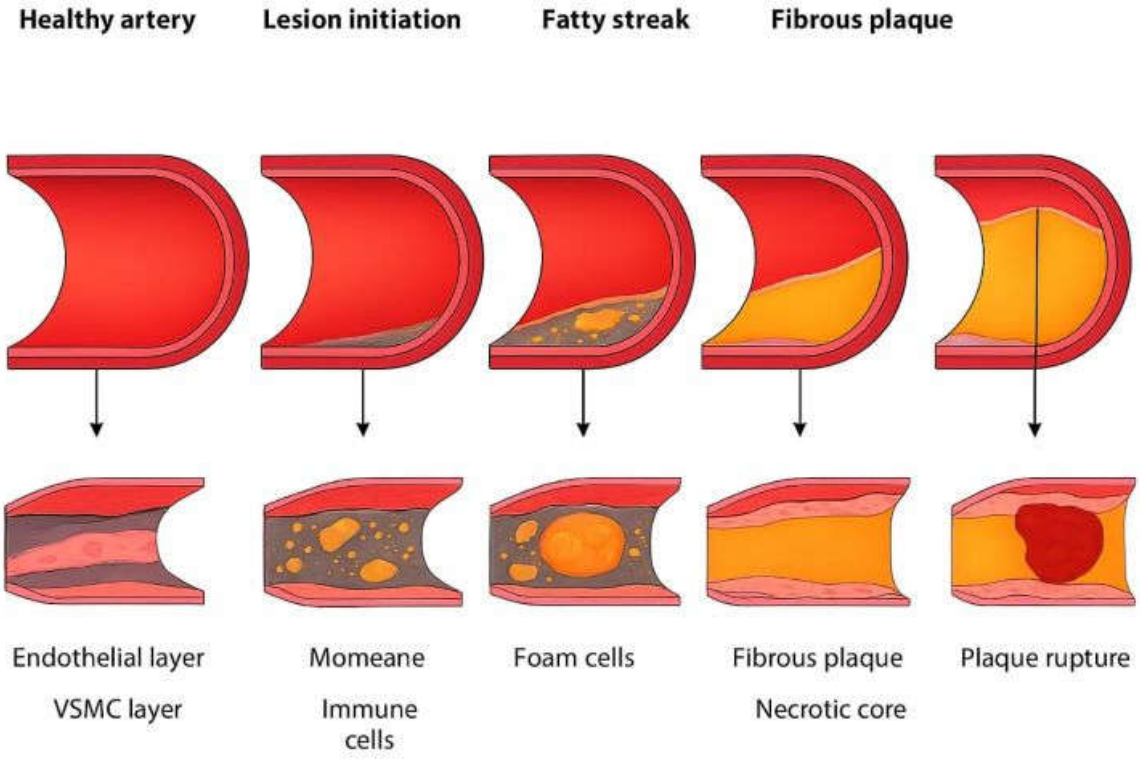

Fig 1: Diagrammatic Representation of Pathophysiology of Atherosclerosis

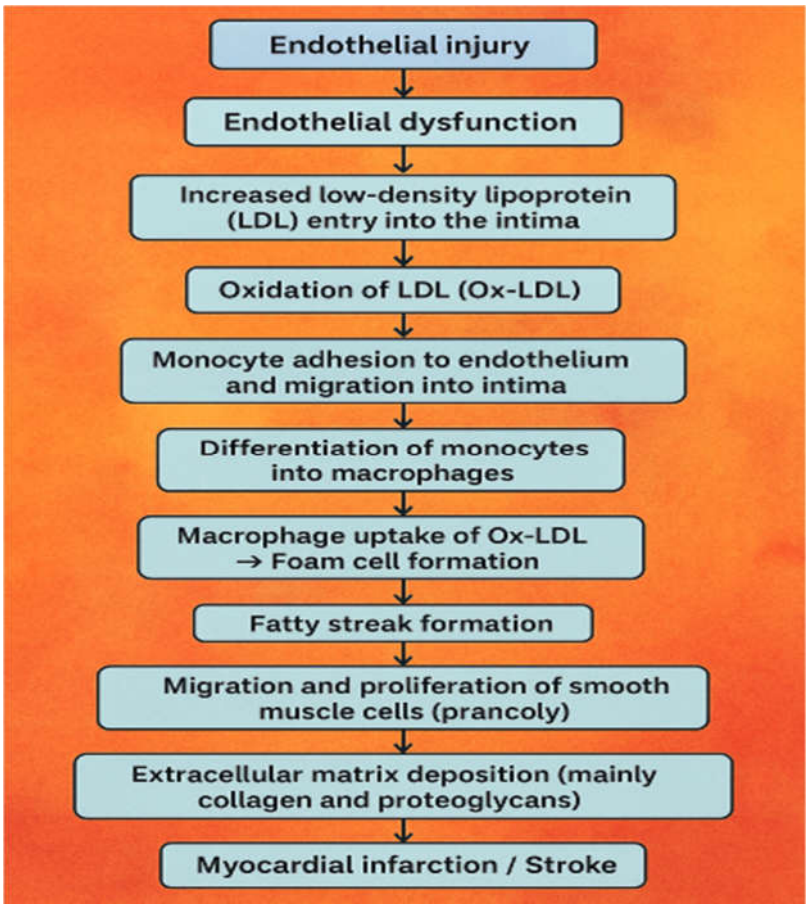

Fig 2: Schematic Representation of Pathophysiology of Atherosclerosis

BIOMOLECULES AND NATURAL PRODUCTS FOR ATHEROSCLEROSIS

Resveratrol

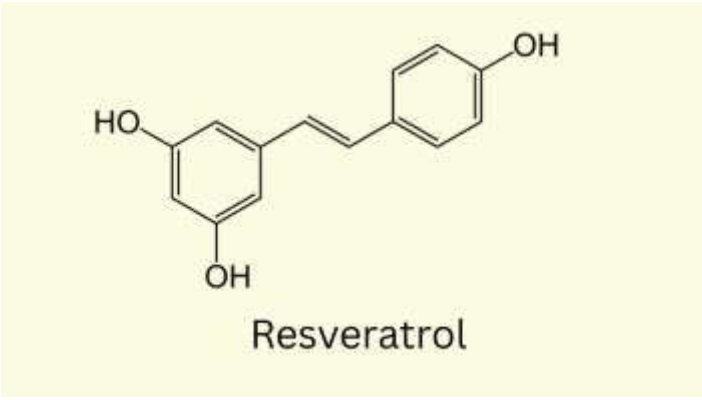

Fig 3: Chemical structure of Resveratrol

In recent years, trans-resveratrol, a polyphenol and the primary grapevine phytoalexin (3,5,4-trihydroxystilbene), has garnered significant attention due to its potent anti-oxidative and anti-inflammatory properties, as well as its potential application in the prevention or attenuation of atherosclerosis and treatment of vascular disease(Slevin, M. *et al.,* 2012, Csiszar, A.*etal.,* 2011).At physiological doses, resveratrol or even red wine alone might considerably decrease TNF-α-induced reduction in the number of endothelial cell progenitor (EPC) cells, which could have a beneficial effect on the re-endothelialisation of damaged arteries. (Maria Luisa Balestrieri*etal.,* 2008).It has been demonstrated that resveratrol inhibits collagen-induced human platelet aggregation and simultaneously causes platelet apoptosis by activating caspases-9, 3, and 8 as well as cleaving gelsolin and actin. (Lin KH*etal.,* 2009).

***Salvia miltiorrhizaBunge* (Lamiaceae)**

Rosmarinic Acid

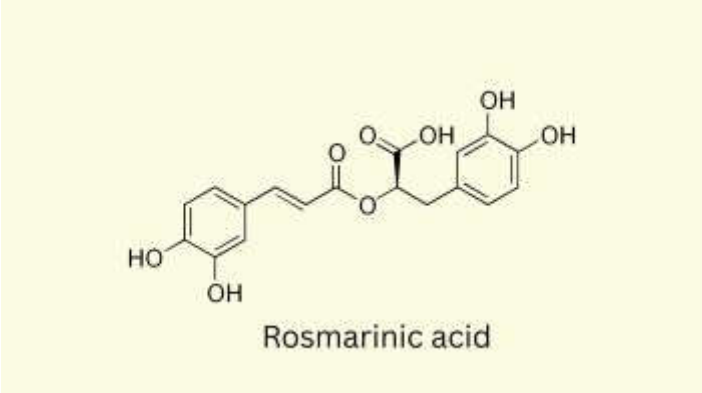

Fig 4: Chemical structure of Rosmarinic Acid

S. miltiorrhiza contains a polyphenol called rosmarinic acid, which has anti-inflammatory, anti-oxidant, and insulin-sensitising qualities. According to a study by Nyandwi JB *et al.,* rosmarinic acid reduces IL-1β secretion by inhibiting NLRP3 inflammasome activation and downregulating the p38-FOXO1-TXNIP pathway (Nyandwi JB *et al.,* 2020).

Quercetin

Fig 5: Chemical structure of Quercetin

Quercetin, sometimes referred to as meletin or quercetin flavonoids, is a naturally occurring flavonoid metabolite that has been shown to be therapeutically effective in treating a number of illnesses, including vascular problems, inflammation, and hypertension. Itspharmacological significance is noteworthy and has great promise, especially in the treatment of cardiovascular disorders. Quercetin can reduce the development of AS plaques by regulating lipid metabolism and reducing inflammatory reactions, according to numerous studies (Garelnabi M*etal.,* 2014, Hua Z *et al.,* 2025).

Notoginsenoside R1

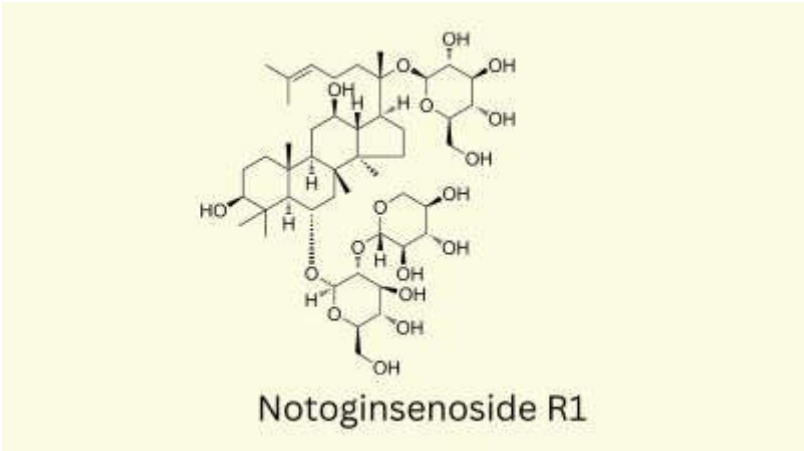

Fig 6: Chemical structure of Notoginsenoside R1

One of the main active metabolites of the total saponins present in P. notoginseng is notoginsenoside R1. Notoginsenoside R1 has positive effects on a number of cardiovascular

illnesses, including those associated with AS. Through anti-inflammatory and anti-apoptotic pathways, energy metabolism modification, oxidative stress inhibition, myocardial fibrosis suppression, antiarrhythmic effects, vasodilation, and angiogenesis stimulation.Notoginsenoside R1 has been shown in animal studies to exhibit anti-AS properties along with a decrease in pro-inflammatory cytokines such as IL-2 (Jia C *et al.,* 2014).

***Coptis chinensis*(Ranunculaceae)**

Berberine

Fig 7: Chemical structure of Berberine

The main metabolite of *C. chinensis* Franch is berberine, also referred to as berberine alkaloid. Berberine has long been used as an over-the-counter drug in therapeutic settings to treat diarrhoea in China. As contemporary research has advanced, new pharmacological characteristics of berberine have continuously been discovered, exposing its wide variety of biological activities that demonstrate its effectiveness in reducing inflammation and AS. Several studies have demonstrated berberine's remarkable anti-AS properties (Li X*et al.,* 2021, Ma CY *et al.,* 2021).

Berberine's therapeutic promise in the treatment of AS is further supported by its demonstrated capacity to regulate the release of pro-inflammatory cytokines.Berberine's ability to control inflammation and plaque composition accounts for its effectiveness as an AS therapy. (Jia D*etal.,* 2022). By activating the AMPK/mTOR signalling pathway, berberine administration caused autophagy and reduced inflammation in J774A.1 cell. Notably, this

study offers fresh perspectives on the therapeutic potential and molecular processes of berberine in the treatment of AS (Fan X *et al.,* 2015).

***Linum usitatissimum* (Linaceae)**

Phenolic substances, protein, carotene, anthocyanin, flavonoids, estrogen, vitamins E and C, proline, and fibre are all found in *Linum usitatissimum*. Alpha-linolenic acid, lignans, dietary and protein fibres, minerals, vitamins, and unsaturated fatty acids, primarily omega-6 and omega-3 at a 0.3/1 ratio, can all be found in *L. usitatissimum* seed. The fatty acids of L. usitatissimum essential oil contain linolenic acid, which has beneficial effects on lowering cholesterol, LDLT, atherosclerosis, and related heart disease (Brouillard *et al.,* 1982)

Omega-3 fatty acid

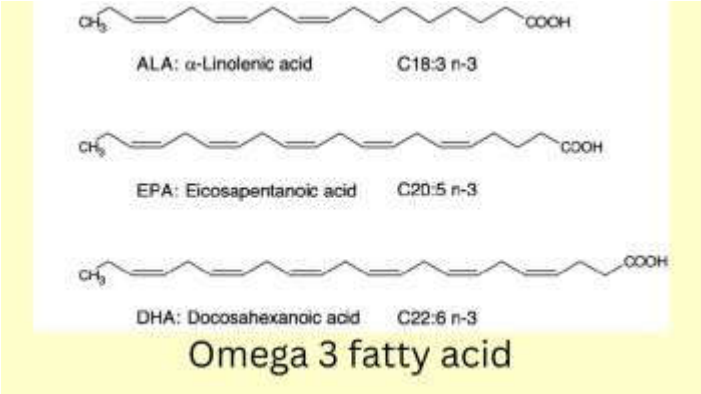

Fig 8: Chemical structure of Omega-3 fatty acid

The fatty acid content from flax seed assists in numerous metabolic functions of the cell, namely, cell membrane structural components and storage lipids. Omega-3 fatty acids and lignans, which have both hypolipidemic and antioxidant properties, are among the compounds responsible for flaxseed oil's hypocholesterolemic impact (Al-Madhagy S *et al.,* 2023).

It has been determined that flaxseed is an important source of omega-3 (n-3) fatty acids. α-linolenic acid (ALA) is abundant in flaxseed. ALA has been reported in various epidemiological investigations as having strong favourable benefits vs heart disease. Incorporating flaxseed or its derived components into the diet can reduce arrhythmogenesis during ischemia-reperfusion, inhibit atherogenesis, and protect against vascular dysfunction under hypercholesterolemic circumstances (Dupasquier CM *et al.,* 2007)

Camellia Sinensis

Polyphenols

There is mounting evidence that oxidative stress, inflammatory factors, and dyslipidemia play a major role in the pathophysiology of diabetes and the development of associated complications. Atherosclerosis and cardiovascular disorders are more common in people with diabetes mellitus due to a number of causes, including increased production of oxygen-free radicals, which raises blood sugar levels and intensifies lipid peroxidation. In this sense, a large percentage of the population, particularly the elderly, suffer from cardiovascular issues brought on by illnesses, particularly metabolic conditions like diabetes mellitus, obesity, and hyperlipidemia. Strong antioxidant molecules may be found in green tea (Camellia sinensis), a popular beverage in Asian nations. Polyphenols such as (−)-epigallocatechingallate (EGCG), (−)epigallocatechin, (−)epicatechingallate, and (−)epicatechin are abundant in it. As bioactive substances with anticancer, antidiabetic, antiviral, antimalarial, hepatoprotective, neuroprotective, and cardioprotective properties, these polyphenols have lately drawn medical interest (Manian R *et al.,* 2008)

Sesamum Indicum Linn

Sesamolinol And Sesamin

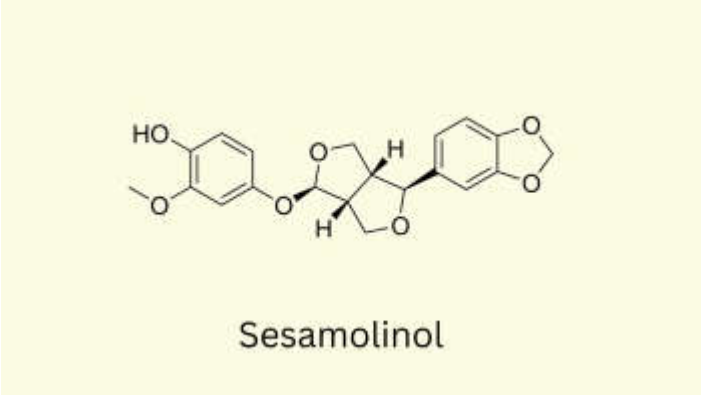

Fig 9: Chemical structure of Sesamolinol

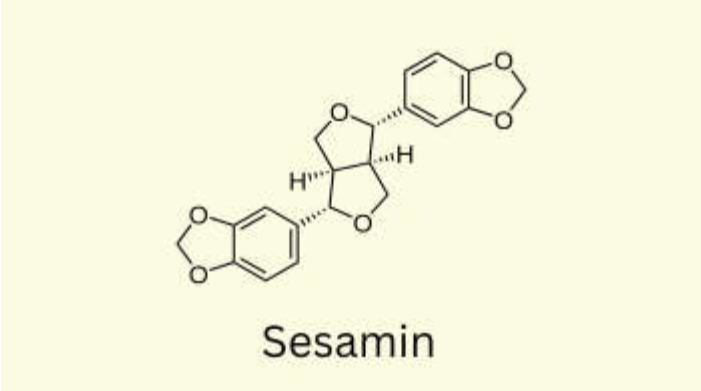

Fig 10: Chemical structure of Sesamin

Sesamum indicum components lower plasma triglyceride and cholesterol levels, LDL-cholesterol (LDL-C), and the formation of atherosclerotic lesions. The formation of atherosclerotic plaques may be aided by *S. indicum's* anti-inflammatory and antioxidant qualities as well as its beneficial effects on lipoproteins. The most prevalent lignans with antioxidant properties in *S. indicum* are sesamolinol and sesamin(Sedighi *et al.,* 2017). Additionally, lignans included in sesame oil are known to remove cholesterol from the stomach and inhibit its absorption. It is impossible to overlook the lignans' role in the observed decrease in plasma cholesterol. The majority of cooking oil's anti-atherosclerotic properties have been linked to its fatty acid desaturation. Olive oil's anti-atherosclerotic properties have been linked to both the antioxidant properties of its polyphenol components and its monounsaturated composition. Sesame oil and sunflower seeds have similar fat contents; however, sesame seeds have equal quantities of monounsaturated and polyunsaturated fat. Sesame oil is high in MUFAs and PUFAs since it includes around 47% oleic acid and 39% linoleic acid (Bhaskaran S *et al.,* 2006).

Sesamol, a lignan found in the sesame oil, is a crystalline solid that is mildly soluble in water. Sesamol's molecular weight is 138.12 g/mol, and its formula is C7H6O3. Sesame oil, extracted from sesame (*Sesamum indicum*) seeds, has been demonstrated to influence lipid metabolism and inflammation, critical processes implicated in the development of atherosclerosis. Numerous studies have shown that taking sesame oil orally lowers LDL and total blood cholesterol levels while raising HDL cholesterol levels. A diet high in sesame oil lowers triglycerides, total plasma cholesterol, LDL cholesterol, and VLDL cholesterol while raising HDL cholesterol in LDLR (Majdalawieh AF *et al.,* 2015).

***Curcuma Longa*(Zingiberaceae)**

Curcumin

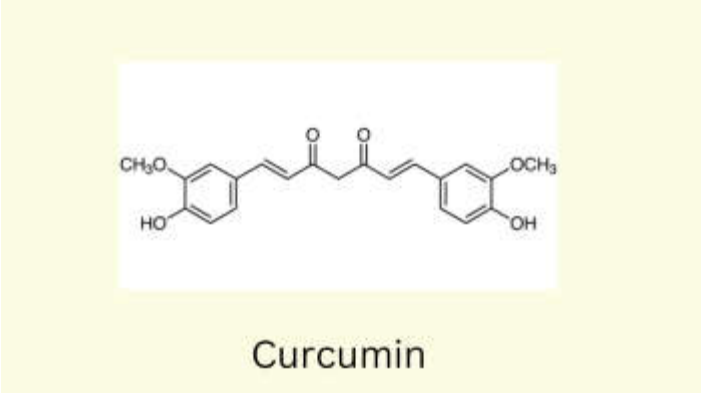

Fig 11: Chemical structure of Curcumin

Curcumin's potential to prevent a number of diseases, including atherosclerosis, has been extensively evaluated. Curcumin has been shown in numerous studies to have strong therapeutic potential in reducing the production of foam cells, controlling pro-inflammatory reactions, adjusting cholesterol efflux, and modifying macrophage polarisation. Curcumin's anti-atherosclerotic effects are molecularly targeted by the upregulation of miR-126, which further suppresses signal transduction and the activation of PI3K/AKT and JAK2/STAT5 (Singh L *et al.,* 2021).

***Punica Granatum*(Lythraceae)**

Ellagic Acid

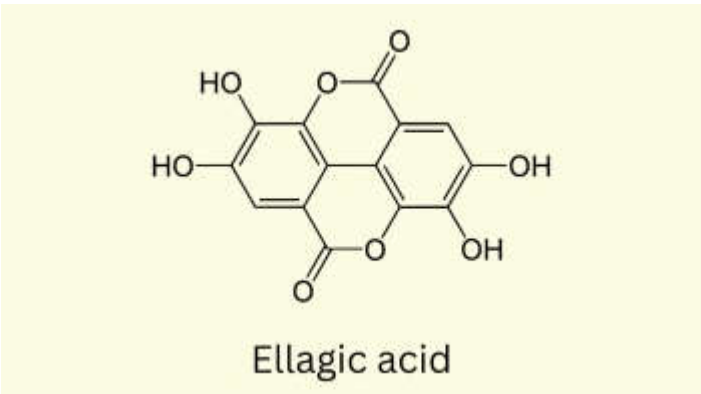

Fig 12: Chemical structure of Ellagic Acid

Numerous plant foods, such as berries, almonds, and pomegranates, contain the polyphenol ellagic acid. Ellagic acid is found in plants as ellagitannin, which is ellagic acid attached to a sugar molecule (Lee WJ *et al.,* 2010). By lowering the lectin-like oxidised LDL receptor-1-mediated signalling cascade, ellagic acid halted oxidised LDL-induced endothelial damage. Interestingly, pomegranate phenolics of punicalagin, punicalin, gallic acid, and ellagic acid enhanced cellular paraoxonase 2 activity and reduced atherosclerotic lesions in peritoneal macrophages of atherosclerotic apoE-deficiency and J774A1 macrophages. Transcriptional pathways related to PPARγ-LXRα signalling may be responsible for ellagic acid's capacity to increase ABCA1-mediated cholesterol efflux from lipid-laden foam cells. Nevertheless, it was discovered that ellagic acid may contribute to ABCA1 activation without PPARγsignalling. (Park SH *et al.,* 2011)

MARKETED FORMULATIONFOR ATHEROSCLEROSIS

Artichoke

The artichoke (*Cynara cardunculus* var. *scolymus* L.), a staple foodstuff and the first cultivated artichoke variety in the Mediterranean area, belongs to the Asteraceae family. Only the heads (flowers) and, to a lesser extent, the stems are edible; the remainder of leaves, stalks, roots, and seeds are also present. Approximately 1500 Kt of it is produced globally. Artichoke by-products (ABPs) are particularly rich in carbohydrates (cellulose, hemicellulose, and inulin) along with their derivatives (lignin), as well as sterols (stigmasterol and β-sitosterol), polyphenols (mainly CQAs and diCQAs), terpenoids (mono-, sesqui-, and the triterpenes), vitamins (E and C), and, to a fewer extent, carotenoids. Proteins, inulin, and bioactives (phenolic acids, flavonoids, caffeoyl derivatives, and flavones) are most prevalent in the bract. Additionally, the potential effect of ABPs on elevated cholesterol was examined. Because fibre compounds (inulin, arabinans, arabinogalactans, as well as xyloglucans) have swelling properties that may reduce intestinal absorption of lipids, their presence is principally responsible for the impact on lipid metabolism. In fact, consuming a 20% ABP fibre supplement reduces triglycerides (TGs) and total cholesterol, which directly impacts the production of cholesterol in conjunction with LDL and liver lipid buildup (Colombo R*et al.,* 2024).

Artichoke Extract Capsules

Artichoke extract has long been utilised by herbalists as a kind of digestive tonic. Recent studies have demonstrated that artichoke extract promotes healthy digestive function by aiding in appropriate bile flow with fat digestion. Additionally, it has been shown that the flavonoids in artichoke extract, such as luteolin and apigenin, support the health of the circulatory system.

Nattokinase

For more than 2,000 years, Asian countries have consumed natto, a cheese-like food created with soybeans fermented using Bacillus subtilis. It is believed that the Japanese diet of natto has a major impact on longevity. A recent study found that eating a lot of natto was associated with a lower probability of dying from CVD in general together with ischemic heart disease in particular. Numerous studies have demonstrated that the main active ingredient in natto, NK, an alkaline protease containing 275 amino acid residues having a molecular weight of around 28 kDa, has several beneficial effects on cardiovascular health. NK's ability to prevent and treat CVD through a variety of pharmacologic activities (antithrombotic, antihypertensive, anticoagulant, anti-atherosclerotic, and neuroprotective) is its most notable feature. Additionally, NK is a natural drug that can be taken orally, has an extensively shown safety profile, is inexpensive to administer, and clearly offers benefits over other pharmaceutical therapies. NK quickly and effectively breaks down fibrin and triggers the expulsion of tPA, which increases the synthesis of plasmin. Plasminogen activator inhibitor 1 (PAI-1), the primary tPA inhibitor, regulates fibrinolytic activity throughout the fibrinolytic cascade. NK may boost the production of clot-dissolving substances like urokinase and stop the production of thromboxane, which prevents platelet aggregation, through the conversion of prourokinase to urokinase. Additional studies demonstrated that NK's direct antioxidant activity, which reduced lipid peroxidation and enhanced lipid metabolism (inhibition of low-density lipoprotein [LDL] oxidation), prevented arteriosclerosis. Because of its antioxidant, in addition to antiapoptotic qualities, the natto extract had a synergistic impact that inhibited intimal thickening (Chen H *et al.,* 2018).

Centella Asiatica

The clonal, perennial herbaceous creeper *Centella asiatica* (CA) may grow up to 1800 meters above sea level in damp conditions. It is common across India and belongs to the Umbelliferae (Apieceae) family. It is a tasteless, odourless plant that thrives close to water. There are medicinal uses for the entire plant. The primary active components of CA are saponins, sometimes referred to as triterpenoids, which include asiaticosides, including Asiatic acid, madecassoside, madasiatic acid, and centellicum. Tannins (20–25%), essential acid (0.1% with beta-chariophylen, trans-beta-pharnesen, and germachrene D), phytosterols (campesterol, sitosterol, stigmasterol), mucilage, resins, free amino acids (alanine, serine, aminobutyrate, aspartate, glutamate, lysine, and treonine), flavonoids (quercetin and kaempferol derivatives), and an alkaloid (hydrochotine) (Gohil KJ *et al.,* 2010)

Hemostatometry was used to measure platelet reactivity and dynamic blood coagulation in rat abdominal aortic blood to investigate the antithrombotic effects of ten active compounds that were extracted from C. asiatica. Based on hemostatometry studies, Satake et al. discovered that only 3,5-di-O-caffeoylquinic acid showed a potential antithrombotic effect. A previous clinical study found that C. asiatica with Pycnogenol (pine bark extract) increases plaque echogenicity and stabilises the plaque density in asymptomatic individuals' carotid and femoral arteries. The subjects were given daily doses of 450 mg of Centellicum (standardized C. asiatica leaf extract) and 150 mg of Pycnogenol for six months (Razali NNM *et al.,* 2019)

Ryte Cholesto Capsules

This concoction, which is entirely Ayurvedic and herbal, promotes heart and arterial fitness as well as good cholesterol levels. Numerous herbal ingredients found in this tablet are utilized to regulate lipid profiles and safeguard heart health.

ActiveIngredients of RyteCholesto Capsules

Amla	Antioxidant-rich, lowers cholesterol
Arjuna	strengths heart muscles
Garlic	reduces bad cholesterol
Guggul	lowers triglycerides, clears arteries
Shilaji Extract	boost energy, supports circulation
Fenugreek	improves lipid metabolism

Policosanol

Rice bran, sugarcane, apples, grapes, and other naturally occurring materials can all be used to extract and purify policosanol. Policosanol has traditionally been used in functional foods due to its many health-promoting properties, including lowering cholesterol, preventing ageing, regeneration of tissues, cyto-, liver-, cardiovascular, and cerebrovascular protection, and defense in opposition to diabetes, hypercholesterolemia, Parkinson's disease, inflammation, ulcers, and cancer. Policosanol, berberine, red yeast rice, cassia nomame, astaxanthin, and Q10 coenzyme are reportedly available as nutraceuticals that are commonly used to treat disorders including hypercholesterolemia and dyslipidaemia (Shen J *et al.,* 2019).

CONCLUSION

A major contributor to cardiovascular morbidity and mortality globally, atherosclerosis is a complicated, multifaceted illness. Although traditional treatments like statins and PCSK9 inhibitors can reduce low-density lipoprotein (LDL) cholesterol, they do not completely address underlying inflammation, oxidative stress, and immunological dysfunction. The substantial therapeutic potential of biomolecules and natural products in the management and prevention of atherosclerosis is highlighted by the data compiled in this study. Through antioxidant, anti-inflammatory, lipid-regulating, endothelial-protective, and antithrombotic processes, natural biomolecules and nutraceuticals such as resveratrol, quercetin, berberine, omega-3 fatty acids, curcumin, and ellagic acid, among others, demonstrate anti-atherosclerotic properties. Their therapeutic usefulness is further supported by commercially available herbal preparations. All things considered, herbal remedies and nutraceuticals are promising, affordable supplements to traditional atherosclerosis treatment. Reducing the worldwide burden of atherosclerosis and enhancing general cardiovascular health may be greatly aided by incorporating evidence-based natural products into the treatment of cardiovascular disease. To verify their effectiveness, safety, and ideal therapeutic application, more standardised clinical studies are required.

REFERENCES

1. Björkegren JLM, Lusis AJ (2022). Atherosclerosis: Recent developments. Cell. 2022 May 12;185 (10):1630-1645. doi: 10.1016/j.cell.2022.04.004. Epub 2022 May 2. PMID: 35504280; PMCID: PMC9119695.
2. Kannel WB (1998). Overview of atherosclerosis. Clinical therapeutics. 1998 Jan 1;20:B2-17.
3. Rafieian-Kopaei M, Setorki M, Doudi M, Baradaran A, Nasri H (2014). Atherosclerosis: process, indicators, risk factors and new hopes. Int J Prev Med. 2014 Aug;5(8):927-46. PMID: 25489440; PMCID: PMC4258672.
4. Hadipour E, Emami SA, Tayarani-Najaran N, Tayarani-Najaran Z 2023). Effects of sesame (*Sesamum indicum* L.) and bioactive compounds (sesamin and sesamolin) on inflammation and atherosclerosis: A review. Food Sci Nutr. 2023 May 22;11(7):3729-3757. doi: 10.1002/fsn3.3407. PMID: 37457142; PMCID: PMC10345702.
5. Kobiyama K, Ley K (2018). Atherosclerosis: a chronic inflammatory disease with an autoimmune component. Circulation research. 2018 Oct 26;123(10):1118-20.
6. Orekhov AN, Ivanova EA (2017). Introduction of the special issue" atherosclerosis and Related Diseases. Vessel Plus. 2017 Dec 28;1:163-5.
7. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, Tokgözoğlu L, Lewis EF (2019). Atherosclerosis. Nat Rev Dis Primers. 2019 Aug 16;5(1):56. doi: 10.1038/s41572-019-0106-z. PMID: 31420554
8. Luca AC, David SG, David AG, Țarcă V, Pădureț IA, Mîndru DE, Roșu ST, Roșu EV, Adumitrăchioaiei H, Bernic J, Cojocaru E, Țarcă E (2023). Atherosclerosis from Newborn to Adult-Epidemiology, Pathological Aspects, and Risk Factors. Life (Basel). 2023 Oct 14;13(10):2056. doi: 10.3390/life13102056. PMID: 37895437; PMCID: PMC10608492.
9. Burlutskaya AV, Tril VE, Polischuk LV, Pokrovskii VM (2021). Dyslipidemia in paediatricians' practice. Rev Cardiovasc Med. 2021 Sep 24;22(3):817-834. doi: 10.31083/j.rcm2203088. PMID: 34565080.
10. Hong YM (2010). Atherosclerotic cardiovascular disease beginning in childhood. Korean Circ J. 2010 Jan;40(1):1-9. doi: 10.4070/kcj.2010.40.1.1. Epub 2010 Jan 27. PMID: 20111646; PMCID: PMC2812791.

11. Tanaka K, Masuda J, Imamura T, Sueishi K, Nakashima T, Sakurai I, Shozawa T, Hosoda Y, Yoshida Y, Nishiyama Y (1998). A nation-wide study of atherosclerosis in infants, children and young adults in Japan. Atherosclerosis. 1988 Aug;72(2-3):143-56. doi: 10.1016/0021-9150(88)90075-5. PMID: 3214466.
12. HOLMAN RL, McGILL HC Jr, STRONG JP, GEER JC (1958). The natural history of atherosclerosis: the early aortic lesions as seen in New Orleans in the middle of the of the 20th century. Am J Pathol. 1958 Mar-Apr;34(2):209-35. PMID: 13520905; PMCID: PMC1934740
13. Ajoolabady A, Pratico D, Lin L, Mantzoros CS, Bahijri S, Tuomilehto J, Ren J. Inflammation in atherosclerosis: pathophysiology and mechanisms. Cell Death Dis. 2024 Nov 11;15(11):817. doi: 10.1038/s41419-024-07166-8. PMID: 39528464; PMCID: PMC11555284.
14. Renu Virmani, MBBS, MD; Chief Editor:Liang Cheng,MD et.al (2025) Atherosclerosis Pathology, 17 Jun 2025;https://emedicine.medscape.com/article/1612610-overview?form=fpf
15. Bergheanu SC, Bodde MC, Jukema JW. Pathophysiology and treatment of atherosclerosis : Current view and future perspective on lipoprotein modification treatment. Neth Heart J. 2017 Apr;25(4):231-242. doi: 10.1007/s12471-017-0959-2. PMID: 28194698; PMCID: PMC5355390.
16. Jebari-Benslaiman S, Galicia-García U, Larrea-Sebal A, Olaetxea JR, Alloza I, Vandenbroeck K, Benito-Vicente A, Martín C (2022). Pathophysiology of Atherosclerosis. Int J Mol Sci. 2022 Mar 20;23(6):3346. doi: 10.3390/ijms23063346. PMID: 35328769; PMCID: PMC8954705.
17. Falk E 2006). Pathogenesis of atherosclerosis. J Am Coll Cardiol. 2006 Apr 18;47(8 Suppl):C7-12. doi: 10.1016/j.jacc.2005.09.068. PMID: 16631513.
18. Steinbrecher UP, Parthasarathy S, Leake DS, Witztum JL, Steinberg D. Modification of low density lipoprotein by endothelial cells involves lipid peroxidation and degradation of low density lipoprotein phospholipids. Proc Natl Acad Sci U S A. 1984 Jun;81(12):3883-7. doi: 10.1073/pnas.81.12.3883. PMID: 6587396; PMCID: PMC345326.
19. Manish Lamoria MD (2024), Yadav N, Ayana AM. Pathophysiology of Atherosclerosis and its adverse effect: Systematic Review. (2024). *African Journal of Biomedical Research*, *27*(1S), 1526-1538. https://doi.org/10.53555/AJBR.v27i1S.1654
20. Glass CK, Witztum JL. Atherosclerosis. the road ahead. Cell. 2001 Feb 23;104(4):503-16. doi: 10.1016/s0092-8674(01)00238-0. PMID: 11239408.
21. Slevin, M., Ahmed, N., Wang, Q. *et al.* (2012*).* Unique vascular protective properties of natural products: supplements or future main-line drugs with significant anti-

atherosclerotic potential?. *Vasc Cell* 4, 9 (2012). https://doi.org/10.1186/2045-824X-4-9

22. Csiszar A (2011): Anti-inflammatory effects of resveratrol: possible role in prevention of age-related cardiovascular disease. Ann N Y Acad Sci. 2011, 1215: 117-122. 10.1111/j.1749-6632.2010.05848.x
23. Maria Luisa Balestrieri, Concetta Schiano, Francesca Felice, Amelia Casamassimi, Antonio Balestrieri, Lara Milone, Luigi Servillo, Claudio Napoli (2008) Effect of Low Doses of Red Wine and Pure Resveratrol on Circulating Endothelial Progenitor Cells, *The Journal of Biochemistry*, Volume 143, Issue 2, February 2008, Pages 179–186, https://doi.org/10.1093/jb/mvm209
24. Lin KH, Hsiao G, Shih CM, Chou DS, Sheu JR (2009). Mechanisms of resveratrol-induced platelet apoptosis. Cardiovasc Res. 2009 Aug 1;83(3):575-85. doi: 10.1093/cvr/cvp139. Epub 2009 May 7. PMID: 19423619
25. Nyandwi JB, Ko YS, Jin H, Yun SP, Park SW, Kim HJ (2020). Rosmarinic acid inhibits oxLDL-induced inflammasome activation under high-glucose conditions through downregulating the p38-FOXO1-TXNIP pathway. Biochem Pharmacol. 2020 Dec;182:114246. doi: 10.1016/j.bcp.2020.114246. Epub 2020 Oct 2. PMID: 33011160
26. Garelnabi M, Mahini H, Wilson T (2014). Quercetin intake with exercise modulates lipoprotein metabolism and reduces atherosclerosis plaque formation. J Int Soc Sports Nutr. 2014 May 27;11:22. doi: 10.1186/1550-2783-11-22. PMID: 24890098; PMCID: PMC4041042
27. Hua Z, Wang X, Qin LL, Zhu KP, Li DY, Zhang XY, Zhang L, Zhai FT (2025). Plant-derived natural products targeting inflammation in treatment of atherosclerosis. Front Pharmacol. 2025 Oct 2;16:1642183. doi: 10.3389/fphar.2025.1642183. PMID: 41111503; PMCID: PMC12528052
28. Jia C, Xiong M, Wang P, Cui J, Du X, Yang Q, Wang W, Chen Y, Zhang T (2014). Notoginsenoside R1 attenuates atherosclerotic lesions in ApoE deficient mouse model. PLoS One. 2014 Jun 16;9(6):e99849. doi: 10.1371/journal.pone.0099849. PMID: 24933211; PMCID: PMC4059705.
29. Li X, Su C, Jiang Z, Yang Y, Zhang Y, Yang M, Zhang X, Du Y, Zhang J, Wang L, Jiang J, Hong B (2021). Berberine attenuates choline-induced atherosclerosis by

inhibiting trimethylamine and trimethylamine-N-oxide production via manipulating the gut microbiome. NPJ Biofilms Microbiomes. 2021 Apr 16;7(1):36. doi: 10.1038/s41522-021-00205-8. PMID: 33863898; PMCID: PMC8052457

30. Ma CY, Shi XY, Wu YR, Zhang Y, Yao YH, Qu HL, Zhang W, Guo YL, Xu RX, Li JJ (2021). Berberine attenuates atherosclerotic lesions and hepatic steatosis in ApoE$^{/-}$ mice by down-regulating PCSK9 via ERK1/2 pathway. Ann Transl Med. 2021 Oct;9(20):1517. doi: 10.21037/atm-20-8106. PMID: 34790723; PMCID: PMC8576642
31. Jia D, Zhang X, Guo Q, Yang R, Yu H, Zhao M, Shi L, Liu M, Wu A, Zhang D (2022). Efficacy and Underlying Mechanism of Berberine Against Atherosclerosis: A Meta-Analysis in Preclinical Animal Studies. J Cardiovasc Pharmacol. 2022 Sep 1;80(3):476-488. doi: 10.1097/FJC.0000000000001308. PMID: 35881903
32. Fan X, Wang J, Hou J, Lin C, Bensoussan A, Chang D, Liu J, Wang B (2015). Berberine alleviates ox-LDL induced inflammatory factors by up-regulation of autophagy via AMPK/mTOR signaling pathway. J Transl Med. 2015 Mar 15;13:92. doi: 10.1186/s12967-015-0450-z. PMID: 25884210; PMCID: PMC4365560
33. Brouillard R (1982). Chemical structure of anthocyanins. Anthocyanins as food colors. 1982:1-40.
34. Al-Madhagy S, Ashmawy NS, Mamdouh A, Eldahshan OA, Farag MA (2023). A comprehensive review of the health benefits of flaxseed oil in relation to its chemical composition and comparison with other omega-3-rich oils. Eur J Med Res. 2023 Jul 18;28(1):240. doi: 10.1186/s40001-023-01203-6. PMID: 37464425; PMCID: PMC10353157.
35. Dupasquier CM, Dibrov E, Kneesh AL, Cheung PK, Lee KG, Alexander HK, Yeganeh BK, Moghadasian MH, Pierce GN (2007). Dietary flaxseed inhibits atherosclerosis in the LDL receptor-deficient mouse in part through antiproliferative and anti-inflammatory actions. Am J Physiol Heart Circ Physiol. 2007 Oct;293(4):H2394-402. doi: 10.1152/ajpheart.01104.2006. Epub 2007 Jul 6. PMID: 17616740.
36. Manian R, Anusuya N, Siddhuraju P, Manian S (2008). The antioxidant activity and free radical scavenging potential of two different solvent extracts of Camellia sinensis

(L.) O. Kuntz, Ficus bengalensis L. and Ficus racemosa L. Food chemistry. 2008 Apr 1;107(3):1000-7.

37. Sedighi M, Bahmani M, Asgary S, Beyranvand F, Rafieian-Kopaei M (2017). A review of plant-based compounds and medicinal plants effective on atherosclerosis. J Res Med Sci. 2017 Mar 15;22:30. doi: 10.4103/1735-1995.202151. PMID: 28461816; PMCID: PMC5390544.
38. Bhaskaran S, Santanam N, Penumetcha M, Parthasarathy S (2006). Inhibition of atherosclerosis in low-density lipoprotein receptor-negative mice by sesame oil. J Med Food. 2006 Winter;9(4):487-90. doi: 10.1089/jmf.2006.9.487. PMID: 17201634
39. Majdalawieh AF, Ro HS (2015). Sesamol and sesame (Sesamum indicum) oil enhance macrophage cholesterol efflux via up-regulation of PPARγ1 and LXRα transcriptional activity in a MAPK-dependent manner. Eur J Nutr. 2015 Aug;54(5):691-700. doi: 10.1007/s00394-014-0747-3. Epub 2014 Aug 1. PMID: 25081501.
40. Singh L, Sharma S, Xu S, Tewari D, Fang J (2021). Curcumin as a Natural Remedy for Atherosclerosis: A Pharmacological Review. Molecules. 2021 Jul 1;26(13):4036. doi: 10.3390/molecules26134036. PMID: 34279384; PMCID: PMC8272048.
41. Lee WJ, Ou HC, Hsu WC, Chou MM, Tseng JJ, Hsu SL, Tsai KL, Sheu WH (2010). Ellagic acid inhibits oxidized LDL-mediated LOX-1 expression, ROS generation, and inflammation in human endothelial cells. J Vasc Surg. 2010 Nov;52(5):1290-300. doi: 10.1016/j.jvs.2010.04.085. Epub 2010 Aug 8. PMID: 20692795.
42. Park SH, Kim JL, Lee ES, Han SY, Gong JH, Kang MK, Kang YH (2011). Dietary ellagic acid attenuates oxidized LDL uptake and stimulates cholesterol efflux in murine macrophages. J Nutr. 2011 Nov;141(11):1931-7. doi: 10.3945/jn.111.144816. Epub 2011 Sep 21. PMID: 21940512.
43. Colombo R, Moretto G, Pellicorio V, Papetti A (2024). Globe Artichoke (*Cynara scolymus* L.) By-Products in Food Applications: Functional and Biological Properties. Foods. 2024 May 7;13(10):1427. doi: 10.3390/foods13101427. PMID: 38790727; PMCID: PMC11119529.
44. Chen H, McGowan EM, Ren N, Lal S, Nassif N, Shad-Kaneez F, Qu X, Lin Y (2018). Nattokinase: A Promising Alternative in Prevention and Treatment of Cardiovascular Diseases. Biomark Insights. 2018 Jul 5;13:1177271918785130. doi: 10.1177/1177271918785130. PMID: 30013308; PMCID: PMC6043915.

45. Gohil KJ, Patel JA, Gajjar AK (2010). Pharmacological Review on Centella asiatica: A Potential Herbal Cure-all. Indian J Pharm Sci. 2010 Sep;72(5):546-56. doi: 10.4103/0250-474X.78519. PMID: 21694984; PMCID: PMC3116297.
46. Razali NNM, Ng CT, Fong LY (2019). Cardiovascular Protective Effects of Centella asiatica and Its Triterpenes: A Review. Planta Med. 2019 Nov;85(16):1203-1215. doi: 10.1055/a-1008-6138. Epub 2019 Sep 20. PMID: 31539918.
47. Shen J, Luo F, Lin Q (2019). Policosanol: Extraction and biological functions. Journal of Functional Foods. 2019 Jun 1;57:351-60.