A Review on Atherosclerosis and Associated Risk Factors with Biomarkers and Treatment

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Abstract

Atherosclerosis is generally chronic cardiovascular disease characterised by the gradual blockage of blood arteries. It refers to "thinning of the artery's intimal layer and fat deposition." The fibrous coating shields the fatty material in the plaque's inner core. As per WHO, CVD will kill millions of individuals by 2030. People who have one or more risk factors for atherosclerosis, such as hypertension, diabetes, hyperlipidemia, obesity, are more likely to develop it. Traditional risk variables are used in current cardiovascular risk prediction algorithms to evaluate cardiovascular risk. After controlling for established risk variables, several blood-based biomarkers have been found as being related with higher cardiovascular risk. Biomarkers Such as C-reactive protein, Interleukin-1, Interleukin-6, glutamine peroxidase, Paraoxonase, apolipoproteins B and apo A-1, and lipoprotein-associated phospholipase A2 which either alone or in combination, have been added into risk prediction to see whether the inclusion of these biomarkers improves the model's prognostic abilities.

Keywords*:* Atherosclerosis, cholesterol, plaque, Biomarkers,

1. INTRODUCTION:

Cardiovascular disease (CVD) continues to remain the leading cause of death in the United States with over 900,000 deaths in 2016 and 17.9 life's each year.[1] CVDs are a group of disorders of the heart and blood vessels and include coronary heart disease, cerebrovascular disease, rheumatic heart disease and other conditions. More than four out of five CVD deaths are due to heart attacks and strokes, and one third of these deaths occur prematurely in people under 70 years of age. Different types of diseases will fall under cardiac problems are Atherosclerosis, Coronary artery disease, Cardiomyopathy, Congestive heart failure. Atherosclerosis forms the cornerstone of CVD, serving as the pathophysiologic mechanism for ischemic heart disease, stroke, peripheral arterial disease and aneurysm formation. Atherosclerosis is a chronic vascular disease which involves the progressive occlusion of blood vessels. [2] The term "atherosclerosis" comes from Greek and means "thickening of the intimal layer of arteries and fat accumulation." The fibrous covering protects the fatty substance in the plaque's central core. Atherosclerosis is divided into two parts: atherosis means fat build-up which is accompanied by numerous macrophages and sclerosis that is fibrosis layer composed of smooth muscle cells, leukocytes, and

connective tissue.[3] Atherosclerosis is a complicated disease characterised by arterial damage, lipid accumulation, platelet and fibrin accumulation, and cellular migration and proliferation. [4] Lipid metabolism disorder is the pathological basis of atherosclerosis, and it is characterized by the accumulation of lipids and complex sugars, hemorrhage, thrombosis, the proliferation of fibrous tissue and calcium deposits, and the gradual degeneration and calcification of the middle layer of the artery, which leads to the thickening and hardening of the arterial wall and stenosis of the vascular cavity. Inflammation is a vital self-defense mechanism of the body. Atherosclerosis is a typical chronic progressive inflammatory response disease. Inflammatory factors, which include tumor necrosis factor-a(TNF-a), interleukin-1b(IL-1b) and others, are often highly expressed during the formation of atherosclerotic plaque. Then the plaques grow with the proliferation of fibrous tissues and the surrounding smooth muscle and bulge inside the arteries and consequently reduce the blood flow. Connective tissue production by fibroblasts and deposition of calcium in the lesion cause sclerosis or hardening of the arteries. Finally, the uneven surface of the arteries results in clot formation and thrombosis, which leads to the sudden obstruction of blood flow [1-3].

2. Epidemiological Studies

Furthermore, it is the principal cause of cardiovascular disease, stroke, and peripheral necrosis. In 2019, an approximate 17.9 million individuals died from cardiovascular diseases, accounting for 32% of all global fatalities. 85 percent of these fatalities were caused by a heart attack or a stroke. Globalization, population ageing, cultural change, stress, and inherited factors are also CVD risk factors. Shifting lifestyle habits of the modern society and environmental conditions have led to the development of atherosclerosis at younger ages, with mortality rates due to its complications increasing yearly

Cardiovascular diseases have now become the leading cause of mortality in India, a quarter of all mortality is attributable to CVD. As per WHO, 23.6 million people are expected to die from CVD by 2030.[4] People with presence of one or more risk factors such as hypertension, diabetes, hyperlipidemia, obesity are prone for development of atherosclerosis.

3. Pathogenesis

In pathogenesis of atherosclerosis multiple factors play role most prominent of which are oxidative stress, inflammation and hereditary predisposition, long term studies explain the pathogenesis in detail.[6] In 90s the sir Russell ross explained the pathogenesis as endothelial cell injury and invasion of cells and according to recent studies, atherosclerosis is a persistent inflammatory illness, not a degenerative disease caused by the ageing process as previously thought.[7] Because of current research in the domain of atherosclerosis, understanding of the pathophysiology of

atherosclerosis has become increasingly accessible at both the lipoprotein metabolic and inflammatory molecular levels. Basic pathogenic mechanisms of atherosclerosis include Endothelial disfunction, development of fatty streak, Formation of atherosclerotic plaque.

3.1.Endothelial dysfunction

A healthy artery has 3 layers which are endothelial cell layer i.e., Tunica intima a monolayer of endothelial cells that lines the lumen of all blood vessels, second one is Tunica media forms concentric layers of elastin fibers and VSMC (vascular smooth muscle cells), and extracellular matrix that regulate vascular tone and third layer is tunica adventitia that surrounding layer of connective tissue It is possible that this location is vital for inflammatory and angiogenesis.[8] Naturally functional endothelium release and maintains nitric oxide level the artery wall healthy but is quickly deactivated by blood. Endothelial dysfunction can be caused by a variety of causes, the most significant of which are lifestyle, cigarette use, hypertension, Diabetes mellitus and genetic alteration. Endothelia function via as-yet unknown processes, potentially connected to the synthesis of modified low density lipoprotein in the artery wall this will further lead to formation of atherosclerotic plaque.

3.2.Formation of fatty streaks

According to studies, fatty streaks are the earliest visible indicator of atherosclerosis.[9] The earliest lesions are frequently produced by a localized increase in the lipoproteins of the artery's intimal layer. They are comprised of lipid-containing foam cells that are found in the artery wall right beneath the endothelium. the development of fatty streak happens in four steps LDL trapping, activation of endothelial cells, activation of leukocytes, and formation of foam cells.[10] Normal circumstances result in an equilibrium between the plasma LDL amount and the cellular LDL concentration of artery walls. Most of these particles become stuck in the intima due to an increase in plasma lipids. Normal circumstances result in an equilibrium between the plasma LDL amount and the intracellular LDL amount of artery walls. Many of these particles become stuck in the intima when plasma lipids rise. The entrapment of low-density lipoproteins causes a rise in the amount of LDL in the intima and an elevation in the length of their stay in the lesion, the blood lipid level act as indicator for initiation of atherosclerosis.[11] Cytokines and oxidised lipids play critical roles in endothelial cell activation. Monocytes and T lymphocytes invade the vascular intima during the early stages of atherosclerosis. Endothelial cells begin to manufacture cell surface adhesion molecules such VCAM-1, leading monocytes, and T-lymphocytes to stick to the endothelium and subsequently move beneath it by squeezing between the endothelial cells. Chemoattractant cytokines

attract circulating monocytes and T-lymphocytes to the sites of damage (chemotactic cytokines).[12]
Endothelial cells alter form as well, and tight connections between them weaken, increasing permeability to lipids, fluid, and leukocytes. Lipoprotein particles, particularly low-density lipoprotein, enter and oxidize in the artery wall LDL is oxidised in the artery wall because of exposure to nitric oxide, macrophages, and certain enzymes such as lipoxygenase. Monocytes develop into macrophages after migrating into the intima and begin to pick up oxidised LDL that has gone into the intima. Macrophages retain the lipids they absorb, and when their lipid content increases, they are described to as "foam cells." The foam cell will eventually die due to apoptosis, but the lipid will collect in the intima.[13]

3.3.Formation of atherosclerotic plaque

When adjoining SMC and endothelial cells secrete tiny peptides such as cytokines and growth factors such as interleukin1 and TNF causing serious damage to vascular tissue. smooth muscle cells migrate into the luminal side of the vessel wall because of these causes. Over time, lipid and smooth muscle cells accumulate in the intima, and the expanding lesion begins to lift the endothelium and invade on the lumen of the artery. Smooth muscle cell migration and newly generated extracellular matrix create the fibrous cap in this state. Fibrous cap collagen fibers, SMC, macrophages, and T lymphocytes make up the fibrous cap. They all create the mature atherosclerotic plaque, which bulges into the channel and reduces the blood flow in the arteries. The developed plaque border consists of T cells and macrophages, these macrophages produce meta proteinase which causes lysis of extracellular matrix and TNF -α prevents collagen synthesis in smooth muscle cell which is produced by T cell these all further weaken the formed plaque fibrous cap and may break it down. Breakdown of the fibrous cap reveals collagen and lipids to the bloodstream, which leads to platelet aggregation and adhesion, as well as the development of blood clots, which can unexpectedly block the bloodstream.[14]

4. Risk Factors

When we think of persons suffering from heart disease, we generally think of middle-aged people. In fact, atherosclerotic heart disease is the leading cause of mortality for both men and women in North America, but its influence begins far before maturity.[15] Although the specific etiology of atherosclerosis is unknown, certain characteristics, situations, or behaviors may increase a person's risk of acquiring it. These circumstances are referred as risk factors, and the number of risks factors a person has increases their chances of developing atherosclerosis. Most risk factors can be controlled, and atherosclerosis can be prevented or delayed. These include high cholesterol and LDL in the blood, low level of HDL in the blood, high

blood pressure, Diabetes, tobacco smoke, lifestyle. A familial background of heart disease is another risk factor that cannot be avoided. Atherosclerosis is caused by a combination of non-modifiable and modifiable risk factors. Current treatments focus on modifiable risk factors, such as lifestyle modifications, the management of related disorders including hypertension and diabetes, and the reduction of blood cholesterol concentrations.

4.2. NON-MODIFIABLE

- **AGE**

  As the person grows older, the risk of atherosclerosis rises, and hereditary or lifestyle of particular person lead plaque build - up in the arteries over time. By middle age or later, sufficient plaques have built up to create indications or symptoms; in males, the danger rises after age 45, and in women, the danger rises after age 55.

- **FAMALIAL HISTORY**

  If a family member was diagnosed with heart disease earlier, the risk of developing atherosclerosis increases. However, just because you have one of these risk factors does not mean you will develop atherosclerosis. Even in older persons, lifestyle adjustments and or medications to manage other risk factors can typically minimise genetic impacts and prevent atherosclerosis from forming.

4.3. MODIFIABLE RISK FACTORS

- **DIABETES**
  This is a condition in which the body's blood sugar levels are elevated due to a lack of insulin production or improper insulin usage.

- **DYSLIPOPROTEINEMIA**
  It refers to a group of diseases of lipoprotein lipid metabolism that involve abnormally high and low lipoprotein concentrations, as well as changes in the makeup of these lipoprotein particles.

- **OBESITY**
  Being overweight means carrying excess weight in the form of muscle, bone, fat, and/or water. Obesity is defined as having a large quantity of excess body fat.

- **INSULIN RESISTANCE**
  Insulin is a hormone that aids in the transport of blood sugar into cells for usage, and insulin resistance develops when the body's own insulin is ineffective.

- **BACTEROLOGICAL INFECTION**
  The microbiota or all of the microbes in body, can contribute to atherosclerosis in a variety of ways, including immune system regulation, metabolic alterations, food processing, and the synthesis of specific metabolites that can enter the bloodstream. Trimethylamine N-oxide is one such metabolite generated by gut bacteria. Its levels have been linked to atherosclerosis in human studies, and animal studies show a causative relationship. A link has been discovered between bacterial genes producing trimethylamine lyases, the enzymes involved in the production of TMAO, and atherosclerosis.

- **SMOKING**
  Compounds found in cigarette smoke can activate endothelial NADPH oxidase and increase mitochondrial oxidative stress. Vascular inflammation, DNA damage, and vascular ageing are all caused by increased superoxide and peroxynitrite production. Furthermore, cigarette smoke chemicals cause LDL to undergo oxidative changes, which increases LDL's pro-oxidative activity. Smoking damages and tightens blood vessels, raises cholesterol levels, and raises blood pressure; it also prevents oxygen from reaching the body's tissues.

5. BIOMARKERS

The discovery of atherosclerosis biological indicators is critical for reducing the disease's onset, development, and consequences. Oxidative stress, inflammation, thrombosis and proteolysis, are some of the most commonly investigated markers in connection to the many processes involved in the formation and rupture of atherosclerotic plaque. More accurate risk stratification and treatment selection are anticipated because of the combination of precisely identifying risk variables and biomarkers. Traditional cardiovascular risk factors, however, do not offer information on the occurrence of atherosclerosis in a large proportion of patients, and other specific variables such as inflammation must be evaluated.

5.1. Inflammatory biomarkers

Inflammation is a significant factor in Atherosclerosis's pathogenesis. C-reactive protein and Interleukin -1, Interleukin-6, and Interleukin-8 are the most common inflammatory indicators used to assess early atherosclerosis.

5.1.1. C-reactive protein

C-reactive protein (CRP) is an important biomarker and inflammatory marker produced primarily by the liver in response to interleukin-1, interleukin-6, and tumour necrosis factor alpha. Some studies on AMI patients have found correlations between CRP concentrations and the size and extent of necrosis, as well as prognosis. Despite of CRP's capacity to predict risk in primary and secondary prevention, it has sparked renewed interest since statins can lower CRP levels without decreasing cholesterol. The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction study found that initial CRP concentrations after statin treatment were just as important in predicting cardiovascular events as LDL-C concentrations in predicting cardiovascular events.

5.1.2. Interleukin -1

Pro-inflammatory cytokines are found in the vessel wall, indicating that they have a role in the onset and progression of vascular disorders. The interleukin-1 is a powerful stimulator of cardiovascular cells. Disrupt cholesterol-mediated LDL receptor feedback control, allowing unmodified LDL to accumulate intracellularly causing foam cell production.

5.1.3. Interleukin-6

It increases fibrinogen levels, which is a risk factor for CHD, Subjects with the highest IL-6 levels were 2-5 times more likely than those with the lowest levels to suffer a heart attack, stroke, or other cardiovascular event. The autocrine and paracrine stimulation of monocytes in the artery wall by IL-6 contributes to fibrinogen deposition, which is linked with increased blood viscosity, platelet number, and activity.IL-6 levels were found to be substantial independent predictors of cardiovascular events in hypertensive individuals. Reduces LPL activity and monomeric LPL levels in plasma, which improves lipid absorption by macrophages. Acceleration of early atherosclerosis by increased pro-inflammatory status.

5.2. Oxidative biomarkers

Biomolecules damaged by reactive oxygen species (ROS) and antioxidant enzymes and molecules are the two primary groups of oxidative stress markers. Molecules produced in a reaction with ROS fall into the first group. Some are eliminated or repaired quickly, while others stay in intracellular or extracellular compartments. Oxidative DNA, carbohydrates, proteins, fats are all major targets of ROS in the different molecules of cells. Stable byproducts formed in vivo because of oxidative

processes are frequently used to measure these indicators. Clinically relevant biomarkers for atherosclerosis include catalase, superoxide dismutase, hemeoxygenase, glutamine peroxidase, Paraoxonase and thioredoxin. The total antioxidant state of plasma is also assessed as a factor to determine the overall antioxidant status.

5.2.1. Glutamine peroxidase

Glutathione peroxidases are the primary antioxidant enzymes in many cells, converting hydrogen peroxide to water and lipid hydroperoxides to their corresponding alcohols. Deficiency of is predominantly produced by the liver and is linked to high-density lipoprotein particles, according to two separate studies. In ApoE KO mice, glutathione peroxidases increase atherosclerosis, demonstrating a protective function for glutathione peroxidases in atherogenesis. In diabetic ApoE-KO mice, seleno-organic glutathione peroxidases-mimetics consistently diminish atherosclerotic plaques.

5.2.2. Paraoxonase

Paraoxonase 1, 2, and 3 are members of the Paraoxonase family of proteins, which have overlapping and distinct esterase and lactonase functions and metabolize/hydrolyze arachidonic acid oxidized byproducts. Paraoxonase 1 is primarily generated by the liver and associates with high-density lipoprotein (HDL) particles. HDL-associated Paraoxonase 1 prevents the synthesis of oxidised phospholipids and hence LDL oxidation. In animal models of atherosclerosis, Paraoxonase 2 inhibits LDL peroxidation, decreases oxidative stress in all major vascular cells, and protects against atherosclerosis. Paraoxonase 3 is present in both serum and cells and, like Paraoxonase 1, suppresses LDL oxidation.

5.2.3. Asymmetric dimethylarginine

Excess reactive oxygen species (ROS) has been shown to reduce endothelial nitric oxide (NO) bioavailability and induce endothelial dysfunction. ADMA is an endogenous NOS inhibitor, resulting in decreased NO production. Due to the lower bioavailability of NO, ADMA is a key connection between ROS and endothelial dysfunction. NOS is decoupled from l-arginine by ADMA, which lowers NOS-derived NO generation. There is also evidence that ADMA may promote NOS uncoupling, converting NOS from a NO-producing enzyme to a superoxide-producing enzyme.

5.3. Lipid metabolism biomarkers

The most often utilised lipid metabolic markers are apolipoproteins B and apo A-1, specifically their ratio, and lipoprotein-associated phospholipase A2.

5.3.1. Apolipoproteins B and apo A-1:

Apo-B is a protein component of atherogenic lipoproteins such as VLDL, IDL, and LDL, and so promotes atherogenesis because ApoB and ApoA-I have opposing impacts on atherogenic risk, the ratio of the two values appears to be more beneficial. ApoA-I is a structural protein indicator of risk component of HDL cholesterol that has been linked to a reduction in atheromatous plaques.

5.3.2. Lipoprotein-associated phospholipase A2:

These are mainly prevalent in LDL, with little levels detected in HDL, however it also appears to prefer binding to lipoprotein. Subjects with high levels of Lp-PLA2 in their plasma have an elevated risk of future cardiovascular events. Lp-PLA2 plays an important role in lipid peroxidation. In hypercholesterolemic middle-aged guys, Lp-PLA2 levels predicted coronary events.[16] These are mainly prevalent in LDL, with little levels detected in HDL, however it also appears to prefer binding to lipoprotein. Subjects with high levels of Lp-PLA2 in their plasma have an elevated risk of future cardiovascular events. Lp-PLA2 plays an important role in lipid peroxidation. In hypercholesterolemic middle-aged guys, Lp-PLA2 levels predicted coronary events.[15]

6. New emerging biomarkers in the field

Although large breakthroughs are happening in detection methods, but existence of atherosclerosis is frequently not discovered until the last stage, which manifests as a myocardial infarction or stroke. A sensitive and non-invasive biomarker-based diagnosis approach is required. The latest 'omics' technique, metabolomics-based techniques, bring a new way to biomarker development since the relative quantity of certain metabolites gives a direct functional assessment of an organism's physiological or pathological state.[17] Furthermore, metabolite levels more precisely represent functional levels than previous 'omics' research because metabolic flows are modulated not just by gene expression but also by environmental factors. Choline, taurine, glycine, and glucose were found as possible biomarkers for the early detection of atherosclerosis in research done in apolipoprotein E-deficient (ApoE) mice. Qingbo and colleagues undertook a comprehensive metabolomics-based investigation to evaluate the molecular causes of atherosclerosis in ApoE/ mice. To discover protein and metabolite alterations in atherosclerotic vessels, researchers used both proteomic and metabolomic methods.[18] Taurocholic acid was found as a possible plasma biomarker of early atheromatous plaque development in a diet-induced atherosclerosis hamster model using LC-MS. [19] TNFSF12 (tumour necrosis factor-like weak inducer of apoptosis) belongs to the TNF superfamily. There are indications that this protein may be involved in the pathophysiology of several illnesses such as atherosclerosis, ictus, rheumatoid arthritis, autoimmune kidney injury, acute kidney damage, and cancer. TWEAK can induce proliferation, survival, migration, cell

growth, and death depending on the cell type studied. It can also induce or hinder cell differentiation. Finally, TWEAK can cause the production of a variety of proinflammatory proteins. soluble TWEAK which is released in larger quantities by healthy arteries than by atherosclerotic plaques, as a possible marker of atherosclerosis.[20]

7. Treatments

Currently, one treatment technique for atherosclerosis is to address lipid metabolism problems, which is extensively utilised all over the world. At the same time, researchers are working on ways to combat inflammatory processes in the vessel wall at the cellular level. Attempts to reduce atherosclerosis in the laboratory have tried both broad-spectrum anti-inflammatory and immunomodulatory methods. Over the last several decades, tremendous breakthroughs in the management of cardiovascular (CV) illness, ranging from increased public health consciousness and prevention to advances in percutaneous coronary intervention and stent creation, have lowered the mortality rates of this disease. The majority of the therapies involved the use of herbal medications, which have traditionally been used to treat atherosclerosis and some synthetic drugs to treat this disease which reduces the cholesterol deposition and other protective action

7.1. Natural Treatments

7.1.1. *Elaeocarpus Ganitrus*

Rudraksha, also known as *Elaeocarpus ganitrus Roxb*., is a big evergreen broad-leaved tree. Many pharmacologically and therapeutically important compounds are found in *E. ganitrus Roxb.*, including triterpenes, flavonoids such as quercetin, tannins such as geraniin and 3, 4, 5-trimethoxy geraniin, and indolizidine alkaloids, grandisines, and rudrakine. Atherosclerosis was experimentally produced in New Zealand white male rabbits for 120 days by cholesterol feeding in order to investigate the benefits of 70% ethanolic *Elaeocarpus ganitrus* seed extract (EEGS) against atherosclerosis. The trial was completed, and the treated rabbits had a strong protective benefit by reducing cholesterol deposition and increasing lumen size when compared to the cholesterol-fed group.[21]

7.1.2. *Dracaena cochinchinensis*

One of the renowned traditional remedies, Chinese dragon's blood, the crimson resin of *Dracaena cochinchinensis*, has been used to enhance blood circulation, disperse blood stasis, halt bleeding, reduce pain, and stimulate muscle regeneration. Phytochemical investigations on Chinese dragon's blood have revealed the presence of flavanoids, homoisoflavanoids, terpenoids, steroids, and chalcones, with phenolic chemicals providing the majority of the biological action. The purpose of this study was to evaluate the anti-atherosclerotic effect of Longxuetongluo Capsule (LTC),

which is made from total phenolic compounds in Chinese dragon's blood, in high cholesterol diet (HCD)-induced atherosclerosis model rats. It was discovered that LTC prevents atherosclerosis and fatty liver by controlling lipid metabolism, and the underlying mechanism may be attributed to its anti-inflammation activity, regulation of vascular smooth.[22]

7.1.3. Baccaurea angulate

Baccaurea angulata is a widely distributed underused fruit found throughout Malaysia's Borneo Island and most of Indonesia. The Euphorbiaceae family includes BA fruit. The purpose of this study was to assess the possible health advantages of *Baccaurea angulata* fruit juice on the aorta of diet-induced hypercholesterolemic rabbits, as well as to detect fatty streak buildup and assess the proportion of atherosclerotic lesions accumulated. The researchers discovered that supplementing a high-cholesterol diet in rabbits with only 0.5 mL BA fruit juice/kg rabbit per day not only improved the aortic lipid profile and attenuated aortic fatty streak progress, but also greatly decreased tunica intima layer thickness, significantly reduced atherosclerotic lesion, and maintained endothelial healing after arterial injury.[23]

7.1.4. Anethum graveolens L.

Dill (*Anethum graveolens L.*) is an annual plant that grows throughout Europe, the Mediterranean area, and Asia. This plant has been used in traditional medicine to treat gastrointestinal disorders such as indigestion, flatulence, and stomach colic, as well as for its antibacterial, antifungal, antispasmodic, antisecretory, mucosal protecting, and hypoglycemic properties. A clinical investigation on hyperlipidemic individuals found that taking six dill pills per day for two months lowered blood total cholesterol levels by up to 18%. Dillweed's hypocholesterolemia impact in rats is most likely due to inhibition of HMG-CoA reductase activity, which suppresses endogenous cholesterol production. Dill extract and dill tablet exhibit hypocholesterolemia capabilities through inhibiting HMG-CoA reductase activity, according to research on golden hamsters.[24]

7.1.5. Zanthoxylum heitzii

This plant is being researched as a possible treatment for atherosclerosis and other cardiovascular illnesses. Research on rats with normal cholesterol levels was performed. The rats were placed into six groups, each with ten rats. These five groups were given a high cholesterol diet, whereas the remaining 61 were given a regular diet. The cholesterol-indued rats were also given distilled water supplemented with roughly 300 mg/kg aqueous extract of the plant's stem bark. When the data were assessed in cholesterolemic rats, they were more useful. Atherosclerosis and lipid profile were both reduced as a result of these findings. This study concluded that this plant can be utilised to treat atherosclerosis as a therapeutic agent.[25]

7.1.6. Panax ginseng

The herb ginseng (Panax ginseng) is used to treat cancer, diabetes, hypertension, and atherosclerosis. Ginseng has an impact owing to the presence of ginsenosides. Ginsenosides come in a variety of forms, with Rb1, Rg1, Rg3, Rh1, Re, and Rd being particularly essential in the prevention of atherosclerosis. In one research, atherogenic rats were separated into four groups based on the therapies they received: control, exercise, Korean red ginseng (KRG) therapy, and combined exercise and KRG treatment. The group that received both KRG and exercise exhibited a greater decrease in atherosclerosis than the other groups, according to the findings.

7.1.7. Fermentum Rubrum

Fermentum Rubrum is responsible for the mixing of Hongqu and gypenosides. Both Hongqu and Jiaogulan are excellent traditional Chinese medicines (TCMs) that have been used in China for millennia to treat hyperlipidemia and associated disorders. The goal of this investigation was to see if HG has any anti-atherosclerotic properties. Normal, model, positive control, Hongqu treated (72 mg/kg), gypenoside (total saponin)-treated (20 mg/kg), and three dosages HG-treated (50, 100, and the model group rats were intragastrically delivered a high-fat emulsion and intraperitoneally injected with vitamin D3. In comparison to the model group, the HG-treated groups had significantly improved serum lipid profiles, oxidative stress, and inflammatory cytokine levels, as well as significantly higher liver total antioxidant levels. Furthermore, in the liver and vascular tissue, the expression of genes involved in lipid production and inflammation decreased while that of genes involved in lipid oxidation rose, indicating enhanced health.[26]

7.2. Synthetic Drugs

Once a cholesterol plaque has formed, it is usually permanent. Plaque accumulation may slow or halt with therapy, but lowering the risk factors that contribute to atherosclerosis will also slow or stop the process. Taking cholesterol and blood pressure drugs, as well as eating a nutritious diet, exercising regularly, and avoiding smoking, all help to decrease cholesterol levels in the body. These therapies will not clear blocked arteries. They do, however, reduce the chances of heart attacks and strokes. Certain medications are used to reduce cholesterol levels.

7.2.1. Statins

Akira Endo's discovery of statins in the 1970s revolutionised the treatment of cardiovascular disease. The first research on the Scandinavian Simvastatin showed that cholesterol-lowering medications reduce mortality in patients with past myocardial infraction. Since then, several studies have shown a reduction in MACE

and death. Statins all lower serum LDL in a non-linear, dose-dependent manner, although their absorption, excretion, and solubility vary. Statins target hepatocytes by inhibiting statins' Pleiotropic actions. A crucial regulator of cholesterol production is HMG-CoA reductase. This decrease in intracellular cholesterol synthesis leads to an increase in hepatic LDL receptors, which lowers circulating LDL levels. Reduced oxidised LDL buildup in the artery intima and an unsatisfied inflammatory cascade enhance 'monocyte recruitment and foam cell development, the first and most important phase in atherogenesis. In comparison to lower dosage regimens, studies utilising greater doses of more effective statins that decrease LDL cholesterol by 50% demonstrate additional therapeutic advantages (e.g., PROVE-IT, TNT). In patients with acute coronary syndromes, high-dose statin treatment reduces early risk significantly (e.g., MIRACLE, PROVE-IT). This summary of statin mechanism and pharmacology is the outcome of decades of study that has resulted in today's guideline-altering approach to CVD care.[27]

7.2.2. Fibrates

Fibrates are a class of medications that are safe, affordable, and effective for the long-term therapy of dyslipidemia in a significant number of individuals with a high risk of cardiovascular disease. Fibrates can stimulate gene transcription because they are synthetic ligands for PPAR, which is a ligand-activated transcription factor. PPAR binds to DNA inside particular response regions to convey signals from lipid-soluble substances such fatty acids, eicosanoids, hormones, and vitamins to genes in the nucleus. There are three PPAR genes that have been discovered alpha, delta and gamma. PPARs bind to peroxisome proliferator response elements as heterodimers with the retinoid X receptor (RXR) once activated by binding to their ligand (PPREs). PPAR is mostly found in fatty acid (FA)-metabolizing tissues such the liver, kidney, heart, and muscle. By modulating the expression of genes involved in several metabolic pathways, PPAR activation by fibrates lowers blood triglyceride levels and boosts HDL cholesterol. Despite these benefits, fibrate medication appears to be unsuccessful in individuals with high LDL (150 mg/dL) levels. The fact that fibrates reduce the risk of stroke without lowering cholesterol levels suggests that PPAR activation may have pleiotropic effects on the vasculature, and thus suggests that the therapeutic potential of this class of drugs will evolve in a manner that is strikingly similar to that of statins.[28]

7.2.3. Bile acid sequestrants

Bile acid sequestration has been proven to regulate plasma cholesterol and minimise atherosclerosis in hypercholesterolemic mice in research. Male Ldlr-deficient mice were utilised as controls, and they were given Colesevelam HCl (BAS) and a running wheel (RUN). For 12 weeks, all of the groups were fed a high-cholesterol diet. After that faeces, bile, and plasma were taken. By using echocardiography to measure the number of atherosclerotic lesions in the aortic arch and heart function, it was shown that BAS RUN reduced plasma cholesterol levels, increased fecal neutral sterol and bile acid outputs, and decreased biliary secretions of cholesterol and bile acids. It was determined that the effects of BAS therapy alone and in combination with RUN on cholesterol metabolism, cardiac function, and atherosclerotic lesion size in hypercholesterolemic patients decreased by 78 percent when compared to controls.[29]

7.2.4. Drugs acting by reducing high blood pressure

A continuous increase in arterial blood pressure, regardless of the origin, aggravates and accelerates atherosclerosis in humans and experimental animals, according to a large body of research. Several researchers analysed coronary atherosclerosis in postmortem material from normotensive and hypertensive men and concluded that hypertensive men have more severe coronary atherosclerosis than normotensive men. Hypertension may potentially have a role in atherosclerosis-related thrombotic problems. Experimental research suggests that high blood pressure can trigger coronary thrombosis by rupturing the surface of the atherosclerotic plaque.

7.2.5. Antiplatelets

Certain drugs are used to reduce the risk of blood clots in the treatment of atherosclerosis as for the mechanisms, platelet inhibition with antiplatelet medication could potentially attenuate atherogenesis and gyui(TXA2) production, aspirin (acetylsalicylic acid (ASA) being the active component) increases platelet nitric oxide (NO) synthesis, protects NO from inactivation, and improves endothelial dysfunction. Although aspirin has anti-inflammatory properties, it is unclear if the levels used to inhibit platelet aggregation are adequate to provide anti-inflammatory benefits in humans. Low-dose aspirin lowers vascular inflammation and stabilises or restricts plaque severity in mice, which might be linked to lower fractalkine levels. Aspirin has been demonstrated to lower levels of pro-inflammatory cytokines such as interleukin (IL)-6 and monocyte colony-stimulating factor in humans, as well as protect the endothelium against inflammatory stress. Despite these and other potential preventive benefits, the overall impact on human atherosclerosis is unknown. In terms of thrombosis, evidence suggests that aspirin has antithrombotic effects via affecting the development and stability of fibrin clots. Studies in mice

with a double apoE and P2Y12 deletion genotype demonstrate reduced lesion area, higher fibrous material at the plaque site, and lower monocyte/macrophage infiltration of the lesions in the double knockout animals compared to control apoE/ mice. Clopidogrel, a P2Y12 inhibitor, lowered p-selectin, e-selectin, chemokines protein-1, and platelet-derived neurotrophic levels in atherosclerotic lesions, decreased macrophages and T-cell invasion, and slowed the initiation and progression of a new atherosclerosis.

7.2.6. Colchicine

The first research, published in 1992, demonstrated no advantage for colchicine 0.6 mg BD in lowering vascular restenosis on serial coronary angiography at 6 months in 197 patients who had balloon coronary angioplasty. A second prospective, randomised clinical study including 196 diabetic patients who bare-metal stents had indicated that participants treated with a 6-month course of colchicine 0.5 mg BD had a substantial effect. Colchicine reduced SMC mediated neointimal hyperplasia without affecting vascular elastic recoil, which is the predominant effect following isolated balloon angioplasty. These contrasting results may be due to colchicine reducing SMC mediated neointimal hyperplasia without affecting vascular elastic recoil, which is the predominant effect following isolated balloon angioplasty. Colchicine's effects on reducing secondary vascular injury and inflammation following percutaneous coronary intervention were investigated in a more recent study that included contemporary drug eluting stents.

7.2.7. MicroRNA

MicroRNA is a single-stranded RNA molecule that regulates gene expression at the post-transcriptional level by binding to the 3' and 5' untranslated regions of mRNA. Endothelial cells (miR-126 and -31 control adhesion molecule expression), VSMC (miR-29 targets MMP2 and mediates VSMC migration), macrophages (miR33, inhibition reduces plaque macrophage content), and cholesterol metabolism (miR-122 regulates serum lipid concentration) are all controlled by miRNA variants, which regulate atherosclerosis. The ability to target miRNA expression might lead to new treatment targets for atherosclerosis. Furthermore, circulating miRNA variations might be useful biomarkers for atherosclerosis, with distinct miRNA profiles indicating different stages of the disease.[31]

7.3. Surgical treatments include

Doctors can view and unblock arteries, or provide a conduit for blood to flow around clogged arteries, using invasive treatments.

7.3.1. Angiography

This test can reveal a picture of atherosclerosis-related blockages. It can be done on your heart, brain, or legs' arteries. Because procedure carries some risk, angiography is normally reserved for those who are experiencing symptoms as a result of their atherosclerosis.

7.3.2. Angioplasty

The use of a balloon to open a blockage in a coronary (heart) artery constricted by atherosclerosis is known as angioplasty. This technique enhances the heart's blood flow. Angioplasty entails the use of a balloon catheter and, if necessary, a metal stent to dilate any narrowed or occluded vessel. Balloon catheters are small, empty balloons that are softly inflated to enlarge the space they are placed in.

7.3.3. Stenting

A stent is a metal or plastic tube that is put into the lumen of an anatomic channel or duct to maintain the route open in medicine, and stenting is the process of placing a stent. Stents are utilised for a number of applications, including expandable coronary, vascular, and biliary stents. Metal stents are long-term implants that function as mechanical scaffolds to support the vessel wall and maintain it open.

7.3.4. Bypass surgery

Blood is redirected around a segment of a clogged or partially blocked artery in your heart during bypass surgery. A healthy blood vessel is taken from your leg, arm, or chest and connected below and above the blocked arteries in your heart during the procedure. Blood flow to the heart muscle improves thanks to a new conduit. The cardiac illness that caused the blockages, such as atherosclerosis or coronary artery disease, is not cured by bypass surgery. It can, however, help with symptoms like chest discomfort and shortness of breath.

8. Conclusion

Atherosclerosis begins with endothelial dysfunction, followed by the formation of fatty streaks, the formation of atherosclerotic plaque, and rupture. While the exact cause of atherosclerosis is unknown, and a combination of non-modifiable and modifiable risk factors and several biomarkers are used for elevated levels of a variety of biomarkers are linked to an increased risk of cardiovascular disease. such inflammatory biomarkers, oxidative biomarkers, lipid metabolism biomarkers. The quest for novel biomarkers will allow the discovery of new proteins that may have a function in the progression of the disease. These proteins should have little variability and be able to be examined using established procedures with minimal effort and expense input. group of biomarkers will offer additional information about an

individual's illness severity, as well as overall prognosis and treatment outcome and many drugs are used in the treatment of atherosclerosis which might be natural or allopathic in nature which are mainly focused on reducing the symptoms of atherosclerosis.

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10. Conflicts of interest

There are no conflicts of interest among the authors

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