Atherosclerosis Unveiled: A Comprehensive Analysis of Treatment Strategies

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Abstract:- Hyperlipidemia is a medical condition marked by an increase in one or more plasma lipids, such as triglycerides, cholesterol, cholesterol esters, phospholipids, and/or plasma lipoproteins, such as very low density lipoprotein and low density lipoprotein, as well as lower levels of high density lipoprotein. Plasma lipid accumulation is one of the most important risk factors for cardiovascular disease. The world's leading cause of death and morbidity is atherosclerosis. It is a chronic inflammatory condition. The hardening and loss of arterial stiffness induced by atheromous plaque formation in the artery wall is known as atherosclerosis. Because it takes time for the artery to narrow or close due to clots, atherosclerosis can go years without generating any symptoms appear only when the artery has narrowed or closed severely, cutting off blood flow to various body organs and leading to a slew of other complications. Plaque is made up of various fatty deposits, including cholesterol, cellular waste products, calcium, and fibrin. The heart, legs, brain, arms, and kidneys all have plaque. They can cause coronary heart disease, angina pectoris, carotid artery disease, and chronic renal disease, among other things. The chance is determined by a combination of acquired and inherited risk factors. This article will begin by providing basic information on the current level of knowledge regarding atherosclerotic plaque pathogenesis and treatment. For a long time, natural remedies have been one of the most significant methods for the prevention and treatment of cardiovascular disease. Many studies on natural compounds that are beneficial for atherosclerosis have been undertaken in recent decades as research on natural products, particularly medicinal herbs, the situation has improved.

Keywords :- Atherosclerosis, Hyperlipidemia, Herbs, COVID-19

Introduction:-
Hyperlipidemia is one of the leading causes of cardiovascular disease. By the year 2020, CVD is expected to be the leading source of morbidity and mortality.[1,2] The main cause of atherosclerosis which is strongly linked to ischemic heart disease, are hypercholesterolemia and hypertriglyceridemia.[3] Hyperlipidemia is associated with increased oxidative stress, which results in the creation of oxygen free radicals, which can lead to oxidative changes in low density lipoproteins, which play a key role in the onset and progression of Atherosclerosis.[4] Atherosclerosis is a long-term inflammatory condition caused by fat deposition in the endothelium of medium and large arteries. It is the world's leading cause of death.[5] Atherosclerosis is a long-term illness that can start in childhood or early adulthood and manifest itself over several years. Although this is idiopathic, there are a variety of causes, including hypertension, excessive cholesterol, and high triglycerides. Atherosclerosis begins in the three layers of smooth tissue that line the artery walls. There are three layers. The inner single-layered endothelium is known as the intima. The media and smooth muscle layer must withstand high blood flow pressure. The connective tissue is known as adventitia.[6] It is a disease of the arterial wall's intima (the innermost layer of the blood vessel wall) that can affect the aorta and coronary arteries.[7,8,9]. In developing countries, this disease is the leading cause of mortality and disability. Excessive fat consumption, limited mobility, and high blood cholesterol are the most significant risk factors[10]. The first time cholesterol was detected in human atherosclerotic lesions was in 1850 by a German study commissioned by Virsho.[11] The term atherosclerosis comprises two parts: atheros, which is defined by fat buildup and macrophages, and sclerosis, which is defined by a fibrotic layer that includes smooth muscle cells, connective tissue, and leukocytes.[12] Hemodynamic patterns, such as oscillatory or turbulent flow, make particular parts of the vascular tree more susceptible to atherosclerosis. The aorta, coronary arteries, and carotid arteries are common examples of these places, which are commonly near branch points or areas of considerable vascular arch[13]

Pathophysiology of Atherosclerosis:-
The progression of plaque in atherosclerosis is divided into many stages.

1.) Development of a fatty streak:- This could begin as early as the early twenties. This is the first phase in plaque formation, where LDL enters the middle layer, accumulates, and eventually oxidises into pro-inflammatory cells as the amount of LDL in the circulation increases. Inflammatory mediators are activated and secreted by VSMC as a result of this buildup, attracting monocytes, lymphocytes, mast cells, neutrophils, proteoglycans, collagen, and elastic fibres. By becoming macrophages, monocytes in the intima evolve into foam cells. This is the first stage of lipid deposition, and it can be addressed depending on the degree of lipid accumulation[14].

2.) The development of fibroatheroma:- It is first noticed in late adolescence. Foam cells and inflammatory cells play an important part in the progression of atheroma at this stage. The lipid binding capability is increased by proteoglycans secreted from the extracellular matrix. A few cells may die as a result of this process, and the inflammation is exacerbated by the dead cells.[15] All of the dead cells clump together and are covered by a lipid-rich core that takes up nearly half of the artery's diameter, obstructing it.
3.) **Fibroatheroma in the thin cap and rupture**: This is most noticeable in people over the age of 50. Over time, a thin cap forms on the plaque. The cap becomes thin in some regions and may burst, causing thrombogenesis, which is a life-threatening risk. This is most common in the cardiovascular system, and it leads to a variety of disorders. Ruptured caps can be repaired and lead to the buildup of collagen, which can lead to the evolution of atheromatous plaque [16].

4) **Plaque localization**: Following the creation of atherosclerotic plaques, the stability of the plaque is a key element in worsening the situation. Coronary arteries, major branches of the aortic arch, and the abdominal aorta are the most common sites of atherosclerotic plaque [17]. Plaque growth is influenced by hemodynamic parameters such as blood flow velocity and changes in shear stress. While the necrotic core, high macrophage content, low collagen levels, and thin fibrous cap cause plaque rupture, complicating things further [18].

![Pathophysiology of Atherosclerosis](image)

**Fig 1:** Pathophysiology of Atherosclerosis

**Etiology of Atherosclerosis**: The underlying etiology of atherosclerosis has yet to be identified. Many factors however, have been found that contribute to atherosclerosis, including:

- **Propensity caused by genes**: The risk of developing atherosclerosis appears to run in families. Anyone whose close relatives have had atherosclerosis (parents, siblings, uncle and aunts) has the right to take advantage of every opportunity to lower their own risk factors.
- **Abnormal cholesterol levels**: Atherosclerosis is linked to high LDL cholesterol levels in the blood and low HDL cholesterol levels [19].
  - Hypertension [20]
  - Smoking
  - Lifestyle of inactivity
  - Obesity, particularly in the abdominal area
  - Diabetes [19]

Even now, in childhood and adolescence, arteries in Western societies typically show early signs of atherosclerosis. Atherosclerosis is a degenerative, slow-moving disease that normally takes decades to manifest symptoms.
Symptoms of Atherosclerosis:-
There are a variety of symptoms associated with atherosclerosis.
1) Chest stiffness or pressure, as well as pain or discomfort (angina).
2) Breathlessness (dyspnea)
3) Pain in the legs or arms, numbness, weakness, coldness
4) Neck, jaw, back, upper abdomen, or throat pain.
5) Dizziness
6) Fatigue [21].

Risk factor of atherosclerosis:- A risk factor that cannot be altered Because risk factors like age and gender cannot be prevented, modified, or controlled, they are less important in risk factor management.[22]

a.) Age :- Males get CAD at 50–65 years of age, and females about 10 years after menopause. Age is an unmodifiable risk factor for CAD. According to the WHO, coronary artery disease (CAD) is the leading cause of mortality in people over the age of 65, and females account for a large proportion of deaths as they get older. Many countries' ageing populations have accelerated the contribution of coronary artery disease to the overall disease burden [23].
b.) Gender:- Coronary artery disease is the leading cause of death in both men and women worldwide. Despite the fact that females have a ten-year delay in the onset of coronary artery disease compared to males, females' CAD death rates do not rise suddenly after menopause, but rather gradually over the years [24,25].
c.) The history of the family :- Coronary artery calcium is a proxy marker of the existence and severity of coronary atherosclerosis that has been consistently linked to an elevated risk of coronary heart disease in certain cohorts. Even after controlling for established risk factors, Zlot et al. found that a parent's history of CHD is linked to higher carotid intima media thickness [26].

A risk factor that can be changed :- Factors that can be avoided, modified, or controlled in theory. Smoking, a poor diet, impaired glucose tolerance and diabetes, high blood pressure, abnormal blood lipids, and obesity are all major modifiable risk factors [22].

a.) Hypertension is a term used to describe the (blood pressure) :- In many populations, hypertension, one of the most conventional risk factors, has continually been linked to an increased risk of developing CAD.[27] It's possible that hypertension's impact on the beginning of CAD is influenced by a variety of environmental and hereditary factors. It is commonly acknowledged that blood pressure-lowering strategies protect against atherosclerosis by delaying the onset of atherosclerotic lesions [28].
b.) Smoking :- Smoking is a significant contributor to the onset and progression of cardiovascular disease and coronary artery disease [29]. The free radicals produced by smoking cause oxidative stress and enhance LDL oxidation, which causes monocytes and T cells to be recruited, resulting in the development of macrophages as well as other processes that promote atherosclerosis [30].

c.) Diabetes mellitus type 2 :- Diabetes, including its most common form, type 2 diabetes mellitus, is one of the risk factors for coronary heart disease. As a result of population expansion, ageing, urbanisation, rising obesity rates, and other factors and physical inactivity, diabetes mellitus is becoming more common with an estimated 200 million worldwide patients. When compared to individuals without diabetes, patients with diabetes mellitus have more advanced CAD at the time of diagnosis [31].

d.) Obesity :- Overweight is a predictor of coronary artery disease as an independent risk as well as a generator of numerous metabolic syndrome atherogenic process.[32] The increased levels of IL-6 encourage the development of C-reactive protein in the liver, and both of these factors contribute to endothelial dysfunction by lowering nitric oxide levels, which causes vasoconstriction and increased vascular resistance. Even after controlling for other risk variables, this connection remained significant (nonHDL, smoking, hypertension). These findings suggest that obesity accelerates the evolution of atherosclerosis in teenagers and young adults decades before clinical symptoms appear [33].

e.) Dyslipidemia :- The main source of harm to the artery and vascular SMCs is a high level of LDL-C in the blood [34]. Hypercholesterolemia can be caused by abnormalities in the LDL receptor's regulatory processes and a fatty diet, which can lead to atherosclerosis.[30] High-density lipoprotein cholesterol, often known as good cholesterol, prevents LDL from being oxidized [34]. By boosting the activities of antioxidant enzymes such as platelet activation factor, acetyl hydrolase, and paraoxonase, HDL protects against atherosclerosis [35].

Intricacy of Hyperlipidemia:-

Atherosclerosis :- Hyperlipidemia is a key risk factor for heart disease, the leading cause of heart disease. Atherosclerosis is a disease caused by the accumulation of lipids, cholesterol, and calcium in the walls of medium and large arteries, as well as the formation of fibrous plaque [36].

Cardiovascular Disease:- The major cause of coronary artery disease, atherosclerosis, is characterised by the accumulation of excess lipid and the formation of fibrous plaque within the artery wall, resulting in a narrowing of the arteries that supply blood to the myocardium, limiting blood flow and providing insufficient oxygen to meet the heart's needs [37].
Acute myocardial infarction :- A myocardial infarction occurs when oxygen and blood flow are partially or fully interrupted in one or more coronary arteries, causing heart cell damage or death. A burst atherosclerotic plaque could be the cause of the blockage [38].

A cerebrovascular accident or ischemic stroke :- The most common cause of death is a stroke. A thrombus, or a fragment of atherosclerosis block that comes off in a tiny conduit within the brain, is frequently the cause of a stroke [39].

Diagnostics Tools:-

1) Invasive technique for coronary angiography :- The gold standard for diagnosing coronary artery disease (or atherosclerosis of the coronary arteries) is coronary angiography. Blood vessel narrowing and blockages are assessed using this method. An X-ray image is captured while an iodine-based contrast is administered through a catheter into the femoral or radial artery [40] This is a safe and quick approach that can be used during coronary angiography without increasing the price of the procedure [41].

![Invasive Coronary Angiography](image1)

Fig 2 Invasive Coronary Angiography

2) Ultrasonography of the blood vessels :- Intravascular ultrasonography generates high-resolution pictures of vascular anatomy using reflected acoustic energy.[42] Using a sound wave generating catheter, this approach may identify the lumen as well as the intimal, medial, and advential layers of the artery wall. Because the smooth muscle cells in the tunica media do not reflect ultrasound waves, it becomes darker, making it easier to identify the three layers.[43] This imaging modality can be used to identify thin cap fibroatheromas, which are fibrous caps that surround a lipid-rich necrotic core and are rich in macrophages but have few smooth muscle cells.[44] Thin cap fibroatheromas are crucial to evaluate since they are susceptible to plaque rupture but are only mildly to moderately obstructive.[45]

![Ultrasonography of the blood vessels](image2)

Fig.-3 Ultrasonography of the blood vessels
3) **Optical coherence tomography** :- In patients having invasive coronary angiography, optical coherence tomography can provide precise information regarding coronary plaque composition. Near infrared light is emitted directly onto the vessel wall using a fibroplastic wire in this technique [46]. The intensity of the returned light waves is being used to form an image of the vessel wall, which is reflected by the tissues [47].

![Optical coherence tomography](image)

**Fig 4 :- Optical coherence tomography**

4) **Positron emission tomography (PET)**:- In the early stages of atherosclerosis, various imaging modalities can be utilised to assess the inflammatory reactions triggered within the artery wall. In positron emission tomography, $^{18}$F-fluorodeoxyglucose (FDG) is a radiolabeled glucose analogue. $^{18}$F-FDG PET is a powerful method for evaluating vascular inflammation, with a substantial association between macrophage density within plaque and inflammatory sign. Single photon emission tomography (SPECT) tracer rounds have also been examined in inflammatory imaging. $^{18}$F-FDG uptake provides a non-specific marker of inflammation in atherosclerosis. These tracers have longer half-lives and are more commonly available than PET tracers [48].

![Positron emission tomography](image)

**Fig 5:- Positron emission tomography**

**Infections causes atherosclerosis :-**

Bonow *et al*, proposed a hypothesis to explain why people with coronary heart disease (CHD) and other atherosclerotic cardiovascular disease risk factors are more likely to have negative outcomes and die from COVID-19. [49] Cardiovascular disease related disease, aside from COVID-19,continue to the leading cause of death among adults worldwide.[50] By modulating inflammation,vasomotor tone, and blood clotting factors, vascular endothelial cells play a vital role in homostasis maintenance [51]. COVID-19 is rapidly spreading, and it is becoming increasingly clear that it affects the vascular endothelium as well as the entire cardiovascular system. Viral replication itself contribute to the decreased ACE2 regulation, exposing endothelium cells to AngII in the absence of angiotensin 1-7 modulatory effects [52]. In three COVID-19 patients, the virus was found to have integrated into endothelial cells and caused an increase in inflammatory cells [53]. Pre existing cardiometabolic variables probably play a role in the severity of COVID-19 individuals clinical manifestation Endothelial dysfunction is an intermediate conditions. Thus , atherosclerosis which shares risk factor with severe COVID-19 infections including such cardiac troponin and diabetes, is a chronic inflammatory endothelium disease defined by lipid infiltration, deposition, and oxidation, activating and fostering self- sustaining inflammation [54]. Endothelial damage characterizes the early phases of atherogenesis, which is accompanied by the accumulation of numerous modified low density lipoproteins (LDL) and other lipoproteins. Inflammation of the artery wall is a result of this. The adaptive and innate immune system are both implicated in lesion development and plaque characterization, which support and contribute to a pro atherogenic state [55].
According to a large study, SARS-CoV-2 infections can induce cardiovascular difficulties for up to a year after onset, not only during the acute phase [56]. The authors of a study published in nature medicine by Washington state university and the department of veterans affairs medical system in st. Louis found that one year after COVID-19 infection, people had a higher risk of heart disease, including CVD, ischaemic and non ischemic heart disease and heart failure. People who hadn’t been admitted to hospital with COVID-19 were at risk, but the risk increased as the severity of the disease progressed, from all those who had not been admitted to hospitals to those who had been admitted to critical care. Patients with COVID-19 had a 72 percent higher risk of heart failure, a 63 percent higher risk of heart attack, and a 52 percent higher risk of stroke when compared to controls. The researchers built a cohort of 153760 patients who survived the first 30 days of COVID-19 infection between March 2020 and January 2021 using national healthcare datasets from the united states department of veterans affairs [57] According to the researchers, people who have had COVID-19 have a higher risk of cardiovascular disease, and while the best way to avoid cardiovascular problems is to avoid infection in the first place, governments and local systems must be prepared to scope with future major problems [58]. Other variables that may make the heart muscle work harder include electrolyte imbalance and the side effects of some drugs [59]. Angiotensin converting enzyme 2 (ACE2) is found in macrophages, endothelium, cardiac fibroblast, smooth muscle cells, and myocytes in the lungs and heart [60]. SARS-CoV-2 infects the same range of cells in the lab as SARS-CoV [61]. Based on this information, both viruses should behave similarly in vivo based on this information. They can infect pneumocytes and macrophages in the lungs, as well as extrapulmonary tissue that express ACE-2, such as the heart [62]. The ADPP-4 receptor is known for promoting atherosclerotic plaque growth by affecting monocyte movement, down regulating adiponectin and stromal derived factor, and blocking the GLP-1R signalling pathway in venous endothelial cells [63].

**Fig 6**: Coronavirus 2 (SARS CoV-2) and Atherosclerosis

Atherosclerosis is treated by different Ways:-

1) Non - Pharmacological Treatment
2) Pharmacological Treatment
3) By using herbs

**1) Non – Pharmacological Treatment:**

**Diet** :- Dietary therapy aims to lower total and LDL cholesterol levels while maintaining a healthy diet. Patients with borderline high LDL cholesterol (130 to 159 mg/dl) with two or more CHD risk factors, as well as those with LDL values of 160 mg/dl or more, should begin dietary therapy. If just one risk factor for CHD is present, the goal of dietary modification in prevention and treatment is to lower LDL cholesterol to 160 mg/dl and even to less than 130 mg/dl if two or even more risk factors are present [64].

**Weight Reduction**: - Obesity increases cholesterol levels in both the VLDL and LDL fractions, boosts triglycerides, lowers HDL cholesterol levels, increases blood pressure, and promotes glucose intolerance. Weight reduction reduces total cholesterol, as well
as its LDL and VLDL components, triglycerides, and HDL cholesterol [65]. Weight loss improves glycaemic intolerance and lowers blood pressure.

**Exercise:** Regular physical activity can lower VLDL, raise HDL, and lower LDL cholesterol in some people. With regular physical activity, blood pressure is lowered and insulin resistance is reduced with regular physical activity [64]. Individual exercise programmes suited to individual goals, interests, and needs are more likely to be followed by patients. The majority of patients benefit from 30 minutes of aerobic activity four or more times a week that targets large muscle groups [65].

**Smoking:** Tobacco use is linked to a significant reduction in HDL cholesterol levels. Smoking cessation can result in a 30% increase in HDL levels in patients [66].

**Dietary fiber:** Soluble fiber has been demonstrated to lower total cholesterol levels in the majority of cases [64]. Total cholesterol can be reduced by 5 to 6 gm/dl by consuming 3g of soluble fiber per day from oat bran [65].

**Anti oxidant:** Atherogenicity and oxidation of bad cholesterol by oxidation and glycosylation [64]. Vitamins with antioxidant properties, such as vitamin C, vitamin E, and beta-carotene, may protect against atherogenesis. Antioxidant vitamins abound in fruits, dark green, and deep yellow vegetables.

**N-3 Polyunsaturated fatty acids:** N-3 fatty acids, which are polyunsaturated fatty acids present in a variety of fish, have been demonstrated to lower blood triglyceride levels [67]. This impact appears to be secondary to the lower VLDL formation [68].

### 2) Pharmacological Treatment

**Treatment with Drugs**

- **a) Inhibitors of HMG-CoA reductase (Statins):**- Lovastatin, Simvastatin, Atorvastatin, Rosuvastatin
- **b) Sequestrants for bile acid (Resins):**- Cholestyramine, colestipol
- **c) Derivative of Fibric Acid (Fibrates):**- Clofibrate, Gemfibrozil, Bezafibrate, Fenofibrate
- **d) Derivative of Nicotinic Acid (Niacin):**- Nicotinic acid
- **e) Inhibitor of selective cholesterol absorption:**- Ezetimibe

**a) Inhibitors of HMG-CoA reductase:-**

Statins are commonly used to treat hypercholesterolemia and have been associated with a decreased prevalence of coronary causes of death and disability in high-risk people. Statins can reduce cholesterol levels by 20% to 50% and have been linked to a lower risk of coronary mortality and morbidity [69].

**MOA:** These medications are HMG-CoA reductase structural analogues. They work by blocking the rate-limiting enzyme in the manufacture of cholesterol in the liver (HMG-CoA enzyme reductase). Statins lower total cholesterol, LDL, and ApoB levels in the bloodstream by blocking this enzyme. Statins produce a minor increase in HDL levels in the blood and a small drop in plasma triglycerides [70].

**b) Sequestrants for bile Acid:-**

The principal mechanism of lipid degradation in the liver is bile acid synthesis. It is estimated that the adult human liver converts roughly 500mg of cholesterol per day into bile acid. Bile acid is released into the intestine and plays a critical function in the absorption of lipids from the diet [71].

**MOA:** Bile acid sequestrants are positive-charged resins that bind to negative-charge bile acids in the intestines to produce a large insoluble complex that is not absorbed and hence excreted in the stool. When resin is administered, excretion increases tenfold, resulting in a higher transformation of bile acids. Moreover, bile acid sequestrants raise HDL levels [72].

**c) Derivative of fibric acid:-**

These medications in this class resulted in a large reduction in plasma triglycerides as well as a small reduction in LDL cholesterol. The level of HDL cholesterol rises gradually. In angiographic studies, fibrates were found to have a major effect in reducing the evolution of cardiovascular events and lowering the prevalence of atherosclerosis.

**MOA:**

- **Lipoprotein lipolysis stimulation :-** Fibrates are ligands for the nuclear transcription receptor PPAR-alpha. They boosted the expression of lipoprotein lipase (apo) and decreased the expression of apoC-III, a lipolysis inhibitor. Fibrates also raise HDL cholesterol levels by raising apoA1 and apoAII expression [73].

- **Hepatic fatty acid (FA) absorption is increased, while hepatic triglyceride synthesis is reduced :-** Fibres boost the increased formation of lipid carrier protein and acyl-CoA synthase, resulting in increased fatty acid absorption by the liver and decreased fatty acid availability for triglyceride formation [74].

- **LDL particle elimination must be improved :-** Fibrates appear to increase LDL catabolism via a receptor-mediated mechanism; LDL particles were larger and more lipid-rich, and so they had a higher affinity for receptors. Fibates help prevent the production of LDL particles that are slowly digested and potentially atherogenic [75].

- **HDL synthesis increases, and reverse cholesterol transfer is stimulated:-** Fibrates stimulate apoA-I synthesis in the liver, resulting in a rise in blood levels of apoA4 and lipid profile, as well as a more efficient reverse cholesterol transport system [76].

- **d) Derivative of nicotinic acid:-**

Niacin, a type B water soluble vitamin, was the first lipid-lowering drug used to treat hyperlipidemia, and it has been shown to reduce cardiovascular morbidity and death. It lowers total cholesterol, low-density lipoprotein cholesterol, and triglycerides [77].
MOA :- Niacin inhibits hormone-sensitive lipase, lowering triglyceride lipid lysis, the primary source of circulating fatty acids. The liver is often responsible for the synthesis of triacylglyceride from these circulating fatty acids. As a result, niacin reduces the formation of LDL by inhibiting VLDL secretion [78].

e) **Inhibitor of selective cholesterol absorption:**
The progress in the development of ezetimibe, the first of a new class of medications that block phytosterol and cholesterol absorption in the intestine, has improved hypercholesterolemia treatment. It prevents sterol absorption from the intestine while having little effect on ADEK plasma levels [79].

**MOA :-** By blocking the niemann-pick C1-like 1 protein, a human sterol transport protein, ezetimibe specifically reduces cholesterol absorption in the small intestine, resulting in a reduction in the transfer of intestinal cholesterol to the liver. The elimination of cholesterol from the bloodstream is increased as a result [80].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Effect on lipids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhibitors of HMG- CoA reductase</strong></td>
<td>Decrease cholesterol synthesis by inhibition of rate limiting HMG-CoA reductase</td>
<td>LDL Decrease, HDL Increase, Triglycerides Decrease</td>
</tr>
<tr>
<td>Lovastatin</td>
<td></td>
<td></td>
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<tr>
<td>Atorvastatin</td>
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<td>Simvastatin</td>
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<tr>
<td>Rosuvastatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sequestrants of bile acid:</strong></td>
<td>Decrease bile acid absorption, Increase hepatic conversion of cholesterol to bile acids, Increase LDL receptors of hepatocytes</td>
<td>LDL Decrease, HDL Increase, Triglycerides not affected may increase in some</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td></td>
<td></td>
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<tr>
<td>colespitol</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Derivative of Fibric acid:</strong></td>
<td>Increase activity of lipoprotein lipase, Decrease release of fatty acid from adipose tissue</td>
<td>LDL increase may increase LDL when triglycerides is high, HDL increase, Triglycerides decrease</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td></td>
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<tr>
<td>Bezafibrate</td>
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<tr>
<td>Fenofibrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Derivative of nicotinic acid:</strong></td>
<td>Decrease production of VLDL, Decrease lipolysis in adipocytes</td>
<td>LDL decrease, HDL increase, Triglycerides decrease</td>
</tr>
<tr>
<td>Niacin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inhibitor of selective cholesterol absorption:</strong></td>
<td>Blocking the niemann pick C1 – like 1 protein, Reduces cholesterol absorption in small intestine</td>
<td>Decrease cholesterol</td>
</tr>
<tr>
<td>Ezetemibe</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3) **By using Herbs:-**

<table>
<thead>
<tr>
<th>Serial No.</th>
<th>Common name(Botanical name)/ Family</th>
<th>Active Chemical Constituent</th>
<th>Part Used</th>
<th>Mechanism of Action</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>Garlic ( (A. sativum) ) Family: Liliaceae</td>
<td>Flavonoid and kaempferol</td>
<td>Bulbs</td>
<td>Garlic main active compound is called allicin the enzyme allicin can inhibit HMG-COA reductase reducing endogenous cholesterol synthesis</td>
<td>[81,82]</td>
</tr>
<tr>
<td></td>
<td>Plant</td>
<td>Family</td>
<td>Secondary Metabolites</td>
<td>Part</td>
<td>Description</td>
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<tr>
<td>2)</td>
<td>Siahdaneh (<em>N. sativa</em>)</td>
<td>Rannunculaceae</td>
<td>Phytosterol consisting of beta sitosterol, stigmasterol, campsterol, thymoquinone</td>
<td>Seed</td>
<td>Thymoquinone the main active constituent in seed oil, protected organs against oxidative damage induced by a variety of free radical</td>
</tr>
<tr>
<td>3)</td>
<td>Rosemary (<em>R. officinalis</em>)</td>
<td>Lamiaceae</td>
<td>Phenols</td>
<td>Leaves</td>
<td>This can be reduced by lowering the low density lipoprotein levels, administration of antioxidants and to increase the production of the beneficial prostaglandin which inhibit platelet aggregation. Rosemary increases production of prostaglandin E2 and has an antioxidant effect, it may beneficial in atherosclerosis</td>
</tr>
<tr>
<td>4)</td>
<td>Barley (<em>H. vulgaris</em>)</td>
<td>Poaceae</td>
<td>Hordens alkaloids</td>
<td>Seed</td>
<td>It contain high concentration of the mixed linkage β-D-glucans. β-glucan increases small intestinal viscosity due to its lower molecular weight and its tendency to form viscous gummy solution resulting in reduced bile acid and cholesterol or triglyceride absorption thus lowering plasmacholesterol</td>
</tr>
<tr>
<td>5)</td>
<td>Anar (<em>P. granatum</em>)</td>
<td>Punicaceae</td>
<td>Phenol</td>
<td>Kernal essential oil</td>
<td>It contain cyclooxygenase and lipooxygenase which are able to inhibit pro-inflammatory enzymes. The polyphenolic flavonoids inhibit macrophages mediated oxidation of LDL and reduce atherogenesis</td>
</tr>
<tr>
<td>No.</td>
<td>Species</td>
<td>Part(s) Considered</td>
<td>Phenolic substances</td>
<td>Effect of Phenolic substances</td>
<td>Reference(s)</td>
</tr>
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<td>-----</td>
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</tr>
<tr>
<td>6</td>
<td>Soya (G max)</td>
<td>Seed, Lipid</td>
<td>Protein, Isoflavones</td>
<td>Lipid lowering effect is mainly due to isoﬂavones can also bind to estrogen receptors, promoting an estrogen-like activity, thus affecting lipid metabolism directly through the modulation of the lipogenesis or indirectly influencing appetite and energy balance.</td>
<td>[88]</td>
</tr>
<tr>
<td>7</td>
<td>Zaitun (O europaea)</td>
<td>Seed, Fruit</td>
<td>Phenolic and Oleoresin</td>
<td>Oxidized LDL is the most damaging form of cholesterol and can initiate damage to arterial tissue, thereby promoting atherosclerosis, olive leaves have been reported to inhibit platelet aggregation and production of thromboxane A2.</td>
<td>[89,90]</td>
</tr>
<tr>
<td>8</td>
<td>Spiny Amaranth (Amaranthus spinosus)</td>
<td>Leaves</td>
<td>Saponins, Steroids, Flavonoids</td>
<td>It inhibits the LDL oxidation and causes a reduction of generated ROS of cytokine secretion. Hence prevent atherosclerotic plaque and platelet aggregation.</td>
<td>[91]</td>
</tr>
<tr>
<td>9</td>
<td>Orchid Tree (Bauhinia purpurea)</td>
<td>Leaves</td>
<td>Glycosides, Flavonoids, Saponins, Terpenoids, Phenolic compounds, Fatty acids and Phytosterol</td>
<td>It reduces ROS production by inhibiting oxidases reducing the production of superoxide and inhibiting oxLDL formation and reduces platelet aggregation.</td>
<td>[92]</td>
</tr>
<tr>
<td>No.</td>
<td>Plant Name</td>
<td>Family</td>
<td>Constituents</td>
<td>Part</td>
<td>Medicinal Uses</td>
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<td>10)</td>
<td>Guava (Pisidium guajava)</td>
<td>Myrtaceae</td>
<td>Flavonoid, glycosides, Saponin, Phytosteroid and carbohydrate</td>
<td>Leaves</td>
<td>It prevent free radical formation and ultimately decreasing vascular resistance</td>
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<td>11)</td>
<td>Snake jasmine (Rhinacanthus nasutus)</td>
<td>Acanthaceae</td>
<td>Flavonoids, steroids, terpenoids, Anthraquinones</td>
<td>Whole plant</td>
<td>It contain napthaquinone rhinacanthin derivative which pharmacological potential anti inflammatory activity through inhibition of iNOS and COX-2 gene expression against release of nitric oxide, PGE$_2$ and TNF-$\alpha$</td>
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<td>12)</td>
<td>Yonjeh (M. Sativa)</td>
<td>Papilionaceae</td>
<td>Beta carotene, Saponin and vitamin B&amp;E</td>
<td>Seed and aerial part</td>
<td>High dietary intake of beta carotene in vitamin E decreases the risk of atherosclerotic vascular disease. It works by stereospecific interaction with retinoic receptor in artery wall</td>
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<td>13)</td>
<td>Zereshk (B. vulgaris)</td>
<td>Berberidaceae</td>
<td>Berberine</td>
<td>Fruit</td>
<td>It inhibit inflammation and cell proliferation in the treatment of atherosclerosis</td>
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</table>
14) Chay (Csinusis) | Catechin, beta sitosterol, phytosterol, carotenoid | Leaves | Green tea also dramatically increases the antioxidant capability of blood which protect the LDL cholesterol particles from oxidation. [98]

Family: Theaceae

15) Ballot (Quercus) | Gallic acid, malic acid, quercetin | Bark, leaves | It helps to maintain a steady state by removing free radicals created in the body. [99]

Conclusion:
Atherosclerosis is a multifaceted condition that involves lipid oxidation and inflammation. Chest pain, dizziness and weakness may be symptoms of atherosclerosis. The process takes several years to begin and is asymptomatic at first, with symptoms appearing later. Occasionally it does not display any symptom at all, but this leads to additional complications. However, when mild symptoms develop, the stage can be detected. The avoidance of complications could be achieved via checking just the plaque phenotype at various phases. There are a variety of imaging techniques for assessing atherosclerosis in distinct artery beds, each with its own set of strength, limits and indications. There has been a movement in recent decades from atherosclerosis measurement toward the data capture on plaque formation or hemodynamics in imaging technologies. Atherosclerosis and other cardiovascular system disorders are risk factors for COVID-19 development. COVID-19 in turn, can cause heart problems and malfunction. Despite the fact that COVID-19, unlike atherosclerosis is an infectious illness, inflammation and the immune response play a key role in the pathophysiology of disease. At the same time, ACE2, which seems to be a receptor for the SARS-CoV2 virus, play a vital role in the development of atherosclerosis. The primary line of treatment for atherosclerosis is non-pharmacological therapy, including nutritional therapy and exercise. The second line of treatment for atherosclerosis is pharmacological treatment including drugs. The third line of treatment for atherosclerosis is by using herbs, the active ingredients in medicinal plants, such as flavonoids and other phenolic compounds with antioxidant activity can generate free radicals and combat atherosclerosis. Even if they don’t have any indications or signs of high blood lipids, it’s critical to advise patients with other diseases or those with a family background of hyperlipidemia to get a routine lipid profile test.

References:


