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Review Article

Anti-Inflammatory Agents and their Role in Atherosclerosis

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Abstract

Atherosclerosis is a chronic disease, with the process of narrowing and hardening of arteries and accumulation of plaques. Normally, atherosclerosis is related with other cardiovascular disease such as peripheral vascular disease, heart attack, and stroke. Aninflammation plays a key role in the progression and development of atherosclerosis. Majorly dead cells and oxidized form of low density lipoproteins (oxLDL) are present as pro-inflammatory cytokines.

Various therapeutic agents of anti-inflammatory has been evaluated for the treatment of atherosclerosis. Few agents have presented beneficial anti-inflammatory effects on the atherosclerosis and suppress the risk of other cardiovascular disease. The anti-inflammatory properties of niacin, statins, flavonoids, and aspirin are the most satisfactory effects for the treatment of atherosclerosis. The cardiovascular safety of cyclooxygenase-2 inhibitor was already trailed in atherosclerosis patient.

The risk of atherosclerosis can be reduced by lowering the lipid level in the body with the help of anti-inflammatory agents, and to avoid other risk factor such as smoking. This review paper will provide an insight of anti-inflammatory agents which are in current use and arrange a prospect, on the challenges against the development of drugs which target inflammation.

Keywords: Atherosclerosis; Aanti-Inflammatory Agents; Inflammation; Therapies; Mechanism of Anti-Inflammatory Agents; Pro-Inflammatory Cytokines

Introduction

Cardiovascular disease such as atherosclerosis, are the primary cause of death globally and it is not confined to specific group of people [1]. Arteriosclerotic vascular disease (ASVD) or Atherosclerosis is a diffuse and degenerative condition, where the plaque deposition around the walls causes hardening and narrowing of arterie [2]. The plaque consists of lipid, cholesterol crystals, necrotic cells, connective tissue, smooth muscle cells, and inflammatory cells. Atherosclerosis can affect medium to large arteries which includes carotid, coronary, and cerebral arteries as aorta and its branches, renal arteries and other major arteries of extremities [3].

Plaque blocks the passage of blood flow in the arteries to major organs like brain, heart, arms, legs and kidney. Atherosclerosis also leads to some other diseases like peripheral artery disease, coronary heart disease, chronic kidney disease and angina, depending on the site of blocakge [4].

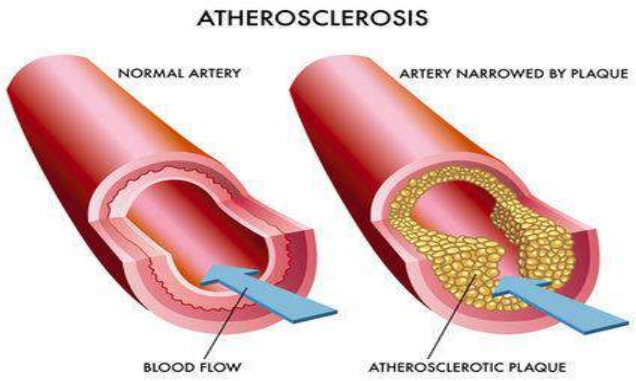

Figure 1. Comparsion between normal artery and plaque in artery [5].

Atherosclerosis is one of the leading chronic inflammatory diseases which raise the mortality and morbidity rate universally [6]. White blood cells (WBC) and fats are macrophages and accumulated in the arteries. WBC plays a vital role in cleaning low-density lipoprotein (LDL) cholesterol pockets. Macrophages plays a wider role because it increases the accumulation of lipids and leads to inflammation and formation of plaque. Fatty streak are the initial signs of atherosclerosis (see figure 2). Fatty streaks were acknowledged by Russell Holman.

This review paper consists of the current information of effects of anti-inflammatory drugs and its therapeutic advantages in the treatment of atherosclerosis.

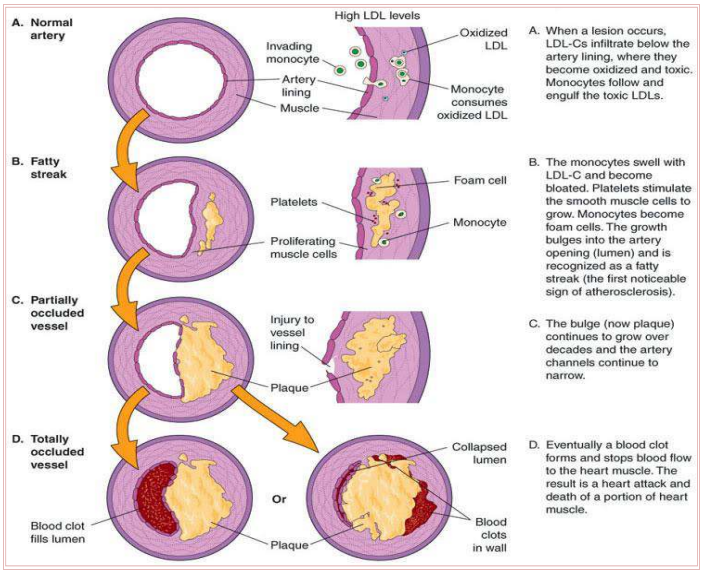

Figure 2. Formation of atherosclerosis plaque in artery [7].

Hypothesis for atherogenesis

There are two different suppositions proposed for the development of atherogenesis.

1) Response to injury: This is initiated by endothelial lining. Due to constant injury to lining, LDL and monocytes derived macrophage gets deposited in to the intimal space. LDL undergoes modification. Monocytes derived macrophage upregulated the modified LDL. Upon up regulation of modified LDL by monocytes derived macrophage, foamy cells are born [6,8,9].

2) Response to retention: Once the LDL gets accumulated in the intimal spaces, the process of modification takes places such as oxidation. Oxidation process can be possible through lipoxygenases, myeloperoxidase, inducible nitric oxide synthase and NADPH oxidases [10]. These modified low-density lipoprotein (LDL) plays a chemoattractant for macrophages and monocytes. Modified LDL will be removed by macrophages with the help of scavenger receptors and gets foamy [11].

The risk factors are classified by every physician such as dyslipidemia, physical inactivity, genetic background, diabetes mellitus, obesity and metabolic syndrome, smoking, hypertension and the mechanism of plaque formation in the intimal space are not fully clarified. There are 70% of cases which are non curable even with established anti-atherosclerotic therapeutics. In addition, 10% of cases observed in healthy human without any pre disposed risk factor [12,13].

Anti-Inflammatory Agents and Atherosclerosis

There are some anti-inflammatory therapies which are used at different stages of atherosclerosis and are described as follow (figure 2):

- Statins (HMG-CoA Reductase Inhibitors)
- IL-1RA antagonists
- IL-6R antagonists
- HDL modulating agents
- Very low dose methotrexate (VLDM)
- Leukotriene antagonists
- Chemokine antagonists
- Regulatory T-cell expansion
- Immunization
- Phosphatase A_2 and ACAT inhibitor
- Chemokine receptor 2 (CCR_2) blockage
- Peroxisome Proliferator-Activated Receptor (PPAR) agonists and Polyunsaturated Fatty Acids (PUFAs).

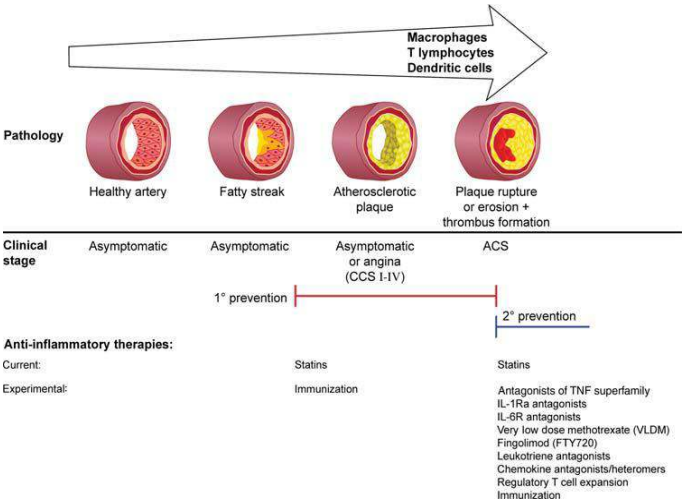

Figure 3. Various anti-inflammatory treatment options for different stages of atherosclerosis [14].

1. **Statins (HMG-CoA Reductase Inhibitors):** Statins (3-hydroxy 3-methyl glutaryl coenzyme A reductase) are the powerful lipid modifying agents. The clinical studies have established the evidence that statins helps to reduce plasma low-density lipoprotein levels with the lower risk of cardiovascular problems which is associated with atherosclerosis [15]. Statins can diminish reactive oxygen species (ROS) generation.The protein subunits of gp91phox and p22phox have statins block expression which regulate the following two activities:

    a. action of NAD(P)H oxidases and

    b. the expression of GTP-ase, an NAD(P)H activator.

This is conducted to suppress the action of pro-oxidant enzymes such as endothelial NOS oxidase, xanthine oxidase, and NAD(P)H oxidase, and decline production of free radicals-peroxinitrite and superoxide anion. The excess production of these radicals is combined with the lower level of NO and developed NO elimination [16,17].

Statins inhibit the HMG-CoA Reductase because at a molecular level, statins and HMG-CoA are similar. Statin takes the place of HMG-CoA and decrease the rate through which it produces mevalonate and later molecule is cholesterol and other compounds. Statin decreases the cholesterol level via various mechanisms such as inhibition of the cholesterol synthesis, increase LDL uptake, and decrease specific protein prenylation [18]. Statin inhibits the pathway of HMG CoA reductase, together reduces the production of specific prenylated proteins and cholesterol [19].

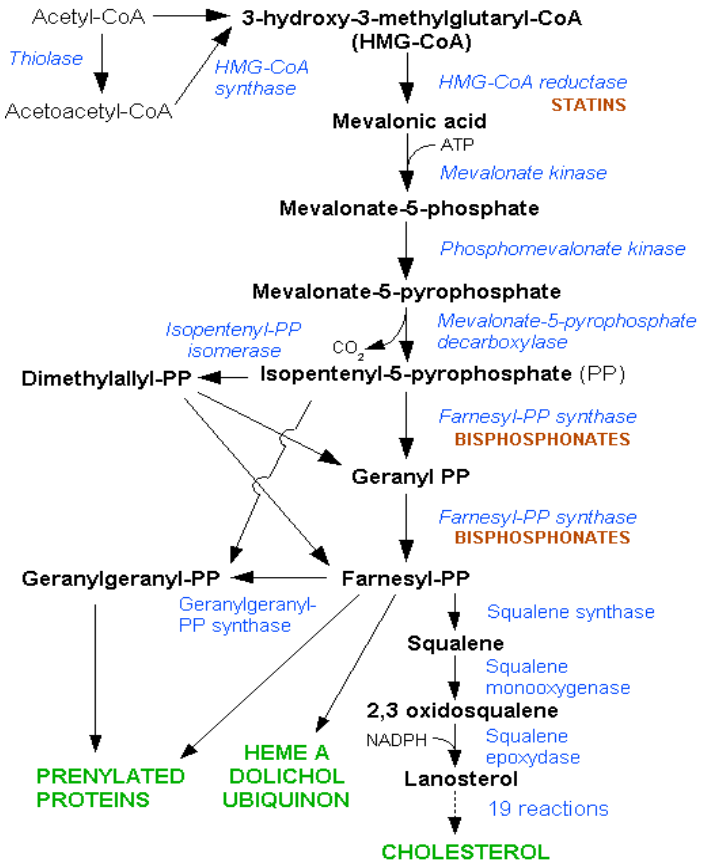

Figure 4. HMG-CoA reductase pathway (Statin blocked the HMG-CoA reductase pathway by inhibiting HMG-CoA reductase enzyme) [19].

Statins (e.g., Simvastatin, Atorvastatin, Cerivastatin, Fluvastatin, Rosuvastatin, Mevastatin) are anti-inflammatory type of drugs which is used in the prevention of primary as well as secondary Coronary Artery Disease (CAD) and along with these anti-inflammatory effects, it also reduces lipids [20]. The sub studies of post hoc C-reactive protein of REVERSAL trials37, A to Z, PROVE-IT TIMI 22 establishes the clinical evidence of statins as the anti-inflammatory effects [21-23] and it also induces the reduction of low-density lipoprotein cholesterol. C-reactive protein were weekly associated with decreased atherosclerosis progression which is independent of LDL cholesterol lowering. The clinical trials (JUPITER) confirmed, the primary prevention of patients by high level C-reactive protein and by low-density lipoprotein cholesterol [24].

Another analysis of JUPITER trials stated that reduction in C-reactive protein correlates with the clinical benefits lineraly [25] and helps in the avoidance of cardiovascular problems. In addition, ARMYDA trials quantified that the administration of high dose of statins to revascularization in Acute Coronary Syndrome (ACS) patients, in turn decreases the cardiovascular problems [26].

2. **Flavonoids:** Generally, flavonoids are the natural substance, which are present in the diet. Recent studies suggests that flavonoids have anti-inflammatory properties which can be used as a therapeutic agent in atherosclerosis treatment. There are a number of mechanisms to describe *in vivo* anti-inflammatory actions of flavonoids like the modulation of proinflammatory molecules production, inhibition of the enzyme which generate eicosanoid, and anti-oxidant activity. Some of the flavonoids work as modulators for the process of proinflammatory gene expression which, leads to diminution of inflammation [27]. There are some mechanism, such as direct radical scavenging activities, antioxidative, modulation of the activities of arachidonic acid metabolism enzymes and nitric oxide synthase, regulation of inflammation-related cells activities, modulation of proinflammatory molecules and gene expression, which explains the anti-inflammatory effects of flavonoids [27].

Among these mechanisms, the direct scavenging of the free radicals can explain the prevention of injury, which is caused by free radical and atherosclerosis. Flavonoid reacts with the reactive group of the radical and stabilizes the species of reactive oxygen. These radicals are inactive, due to the high reactivity of flavonoids, which is having hydroxyl group, according to this equation [28]**:**

Flavonoid(OH) + R• > flavonoid(O•) + RH

Where O• is a free radical of oxygen and R• is a free radical.

There are some flavonoids which can scavenge peroxynitrite, a highly reactive oxygenated radical but specific flavonoids may directly scavenge the superoxides. The radical scavengers are rutin and epicatechin [29]. Rutin have scavenging ability because of its inhibitory activity on xanthine oxidase enzyme. Flavonoids can inhibit the LDL oxidation in vitro [30]. These mechanisms defend the LDL particle and flavonoid performs a preventive role against the atherosclerosis [31].

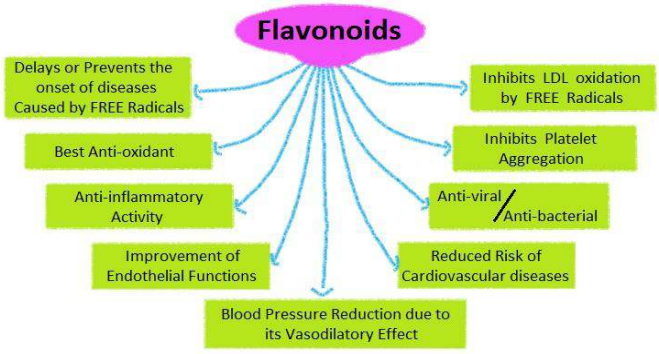

Figure 5. Flavonoids and its different activity [32].

3. **High density lipoprotein (HDL)-Modulating Agents:** Most of the treatment, based on anti-inflammatory agents are dedicated to reduce the low density lipoprotein (LDL) cholesterol levels. When treated with statin, not more than 30% reduction in the relative risk was noticed.

A current study stated that, the increased level of HDL cholesterol does not decrease the chances of cardiovascular diseases in human beings [33]. Different animal studies show the evidence that high density lipoprotein (HDL) cholesterol is protective [34]. High density lipoprotein (HDL) plays an important role in the process of reverse cholesterol transport. In this process, cholesterol is transported to the liver from the peripheral cells, thus at the vascular level, it encourages the transfer of molecule from the lipid-laden macrophages. These HDL particle are involved in the direct anti-inflammatory, anti-apoptotic, anti-oxidative, and anti-thrombotic functions [35]. During the inflammatory activation, HDL particles may switch to the 'dysfunctional' setting, performing on the opposing pro-inflammatory properties. Thus the different functional properties of HDL particles reflect its work than the basic serum concentrations.

Niacin (nicotinic acid) is the most effective agents among all the HDL cholesterol which raises 20-30% HDL cholesterol [36]. Niacin or vitamin B3 is a water soluble vitamin and convert the carbohydrate into glucose, and in turn breakdown to exert energy and it also breakdown the fats and proteins. Niacin acts as an anti-inflammatory agent. It is used for the treatment of atherosclerosis and to diminish the peripheral vascular disease and heart attack. According to some clinical trials, niacin is used for the prevention, cure and treatment of atherosclerosis and evident as most effective medicine for heart disease. Some other studies indicates that the high dose of niacin, may treat the problem of claudication. A recent study stated, that the combination of a simvastatin (statin or HMG CoA reductase inhibitor) and niacin may decrease the risk of heart attack [37]**.**

Niacin binds to the G protein coupled receptors, NIACR1 (Niacin receptor 1) and NIACR2 (Niacin receptor 2), which are highly expressed in keratinocytes, immune cells, spleen, and adipose tissue [38,39]. NIACR1 (Niacin receptor 1) inhibits the production of cyclic adenosine monophosphate (cAMP) and hence fats disrupts from adipose tissue and free fatty acids (FFA) which is available for liver to produce low-density lipoprotein (LDL), very-low-density lipoproteins (VLDL), and cholesterol [40,41]. The hepatic expression of PGC-1b (PPARg coactivator-1b) APOC3 (apolipoprotein C3) suppress along with the free fatty acids and then very-low-density lipoproteins increases and decrease its production [42].

Niacin also inhibits hepatic TG synthesis (diacylglycerol acyltransferase-2) and it develops the apolipoprotein A1 levels because of anti-catabolic effects, which results in the higher reverse transport of cholesterol. Niacin also increases HDL hepatic uptake and production of CETPM gene (Cholesterol ester

transfer protein) [43]. Finally, it triggers ABCA1 transporter in macrophages and monocytes, and up regulate the results of peroxisome proliferator-activated receptor γ (PPAR-γ) in reverse transport of cholesterol [44]. It diminishes increased high density lipoprotein cholesterol (HDL), very low-density lipoprotein cholesterol (VLDL-C), low density lipoprotein cholesterol (LDL), and triglycerides (TG) [43]. Adipocyte produces adipokines mediators and some type of adipokines like as chemokines, interleukins, and tumor necrosis factor (TNF)-alpha are having pro-inflammatory effect. Other such types of adiponectin are having anti-inflammatory effect which regulates the process of inflammation and decrease atherosclerosis and vascular progression [45].

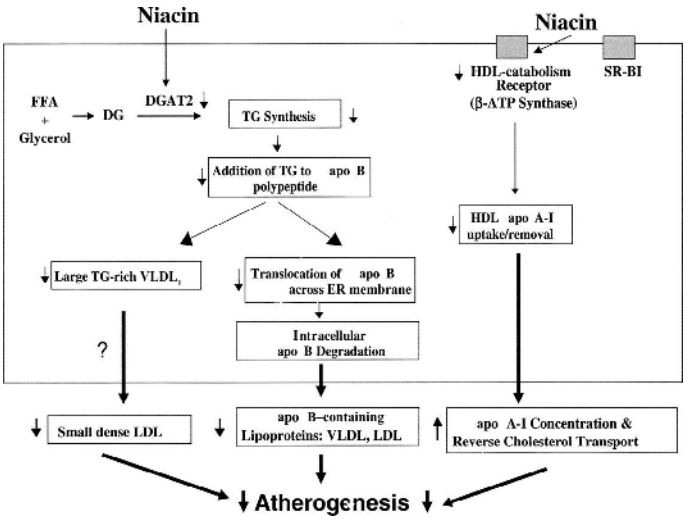

Figure 6. Mechanism of action of niacin in atherogenesis [46].

4. **Anti-platelet agents:** Platelets releases cytokines and chemokine, which characterizes atherosclerotic thrombotic problems by different types of inflammatory activation [47]. The platelets also plays an important role, in the initiation and the early progression of the recruitment of atherosclerosis mediating leukocytes and the adhesion to vascular wall [48]. Recently, a study on platelet activation proposed a relationship, between the risk of thrombosis and increment in the volume of platelets [49]. The addition of CD40 (soluble form) in the sera of human being shows a prediction in atherosclerosis. [48] Aspirin is most commonly used as an anti-platelet drug.

Aspirin with anti-platelet and anti-coagulant effects, helps in the prevention of blood clot formation and it also reduces the probablity of blockage of arteries. Aspirin is an anti-platelet medicine (blood thinner) and having anti-inflammatory activity which helps to diminish the inflammation process. Aspirin also decreases the risk of heart attacks, strokes, and transient ischemic attack (TIA). The most important effects of aspirin are its anti-platelet activity in atherosclerosis [50].

Aspirin inactivates the cyclooxygenase enzyme (COX) or prostaglandin-endoperoxide synthase (PTGs), which is required for the synthesis of prostaglandin and thromboxane. The acetyl group of aspirin binds to a serine residue at the active site of the prostaglandin-endoperoxide synthase enzyme (PTGs). The low dose of aspirin blocks the evolution of thromboxane A2 in platelets, and produces inhibitory effects on the aggregation of platelets. Due to anti-thrombotic activity, aspirin helps in decreasing the rate of heart attacks [51].

There are only two types of cyclooxygenase (COX) enzyme: COX-1 and COX-2. Aspirin inhibit irreversibly to COX-1 enzyme and modify the COX-2 enzyme activity. Generally, COX-2 produces prostanoids, which are proinflammatory and aspirin remolded prostaglandin-endoperoxide synthase-2 (PTGS-2) which produces lipoxins and these are anti-inflammatory in nature [52]. COX-2 inhibitors (Coxibs) act by inhibiting the prostaglandin-endoperoxide synthase-2 (PTGS-2) and reduces gastrointestinal side effects [53]. However, COX-2 inhibitors like rofecoxib (Vioxx), have been recalled from the market recently, after the evidence appear that prostaglandin-endoperoxide synthase-2 (PTGS-2) inhibitor increases the rate of heart attack and stroke [54,55].

5. **Phospholipase A2 and ACAT inhibitors:** Interaction between inflammation and lipoprotein metabolism in atherosclerosis occurs due to the complex phospholipase A2 (PLA2) superfamily. There are five types of enzymes in this family. Among these enzymes, the lipoprotein associated-PLA2 (Lp-PLA2) and secretory-PLA2 (sPLA2) have been combined with the atherogenesis [56]. These enzymes produces lysophospholipids and non-esterified fatty acids (arachidonic acid) by hydrolyzing centre (sn-2) ester bond of phospholipids. Lysophospholipids (lysophosphatidylcholine) are the atherogenic consequences which forms the smaller and denser high density lipoprotein (HDL) and low density lipoprotein (LDL) particles. The low density lipoprotein (LDL) oxidation increases due to the aggregation of vascular low density lipoprotein (LDL), and consecutively, produces inflammatory lipid mediators like leukotriene and prostaglandins [57]. Thus, the inhibitors of PLA2 type have been prepared and they are under phase III of clinical evaluation, in which one for sPLA2 (varespladib) and one for Lp-PLA2 (darapladib).

Acyl-coenzyme A is another important enzyme, which involves in the process of cellular cholesterol metabolism. Acyl-coenzyme A (Cholesterol acyltransferase) (ACAT) is a protein which catalyzes the formation of cholesteryl ester by transferring fatty acyl chain to cholesterol from acyl-coenzyme A. There are two types of isoenzymes, one indicates the macrophages in the atherosclerotic abrasions (ACAT-1) and another isoenzyme indicates the small intestine (ACAT-2). The non-selective phar-

macological inhibition of ACAT suppresses the absorption of intestinal cholesterol and formation of foam cell in the arterial walls. Pactimibe and avasimibe are the non-selective ACAT inhibitors which are developed for clinical use, and shows negative or null results [58]. Recently, K-604: a selective ACAT-1 inhibitor, which have anti-atherosclerotic effects in vitro [59].

6. **Leukotriene pathway inhibitors:** Leukotrienes (LTs) is a sub-class of eicosanoids which exerts a pro-inflammatory smooth muscle constrictive action. Leukotrienes (LTs) involves in allergic and inflammatory disease such as bronchial asthma, inflammatory bowel disease, and rheumatoid arthritis. Initially, montelukast (leukotriene receptor blocker) was injected to the patients who were suffering from acute coronary syndrome for the evaluation of endothelial function in brachial artery (clinicaltrials.gov NCT00351364, data unpublished). Currently, inhibitors of both, 5-lipoxygenase activating protein (FLAP) (veliflapon) and 5-lipoxygenase (5-LO) (atreleuton), were considered in human beings. Atreleuton (5-LO inhibitor) was injected for 24 weeks in patients who were suffering from acute coronary syndrome and result indicated, reduction in the amount of non-calcified plaques and the formation of new coronary plaques in comparison with placebo and a 66% reduction of high-sensitivity C-reactive protein (hsCRP) correlate these effects [60]. In compare to atreleuton, the veliflapon is a weak 5-lipoxygenase activating protein (FLAP) inhibitor, which encourages the reduction of LTB4 production and myeloperoxidase activity with a minor reduction in CRP [61].

7. **CCR2 blockade:** The process of inflammation influenced by chemokine CC motif ligand 2 (CCL2) and it is also well known as monocyte chemoattractant protein-1. Chemokine interacts with chemokine receptor 2 (CCR2) and generates the deposition of blood monocytes which becomes plaque macrophages. MLN1202 (Monoclonal antibody) inhibits the binding of chemokine CC motif ligand 2 (CCL2) and observes chemokine receptor 2 (CCR2). This MLN1202 monoclonal antibody was evaluated in a doubleblind, randomized, and placebo-controlled trials. The major target of this trial was to measure the reduction in high-sensitivity C-reactive protein (hsCRP) along with the treatment of cardiovascular patients [62].

8. **Peroxisome Proliferator-Activated Receptor (PPAR) agonists and Polyunsaturated Fatty Acids (PUFAs):** Peroxisome Proliferator-Activated Receptor (PPAR) is the ligand activated transcription factor which belongs to nuclear receptor family. It is called as transactivation. During transactivation process, Peroxisome Proliferator Activated Receptor (PPAR)/ nuclear retinoid receptor (RXR) heterodimers binds to PPAR response elements (PPREs) of the target genes, and it interferes with different transcription factors such as activator protein-1 (AP-1) and nuclear factor-kB (NF-kB). These factors shows different effects and involves in the regulation of inflammation, vascular tone, and metabolism. Peroxisome Proliferator-Activated Receptor (PPAR) have three isoforms with different function and that are α, γ, and β/δ with corresponding agonist.

PPAR- α agonist (Fibrates) showed beneficial effects on the serum lipids with a reduction in the triglyceride levels, and it causes some simple effects on HDL cholesterol (increase) and LDL cholesterol (decrease). These positive changes are complementary to those which are induced by statins [63].

PPAR- γ agonist (Glitazones) are an anti-inflammatory agent [64] and two molecules of it are available in the market and that are rosiglitazone and pioglitazone. These molecules improved the insulin sensitivity, which showed some therapeutic effect for type-2 diabetes mellitus [65,66]. In vitro, pioglitazone decreases the formation of IL-6, IL-1 β, toll-like receptors (TLRs), MCP-1, and tumor necrosis factor (TNF) – α in human blood monocytes [67] and in vivo, pioglitazone reduces hsCRP level with anti-inflammatory effects in both diabetic and non-diabetic patients. [68].

Omega-3 fatty acids are other drugs which are able to reduce the triglyceride levels. These endeavors to copy Eskimo diet which was the secondary prevention of cardiovascular problems with different anti-inflammatory effects and it also involves in the previously mentioned mediators resolvins [69].

9. **Succinobucol and fasudil**: The blockage of oxidative stress or oxidation of lipoproteins is another approach for the treatment of atherosclerosis [70]. There are two drugs, succinobucol and fasudil, which produces in-vitro anti-oxidant effects in atherosclerosis patients. Succinobucol is a subordinate of probucol which was withdrawn due to the safety reason at phase III evaluation and it was proven to have anti-oxidant and anti-inflammatory effects in the endothelial and blood mononuclear cells [71]. The ARISE clinical trials investigated that the succinobucol have effects for an acute coronary syndrome in cardiovascular patients. In acute coronary syndrome, there is no variation in the primary end point (Myocardial infraction, coronary revascularization, unstable angina, resuscitated cardiac arrest, stroke, or cardiovascular death) and other composite secondary end point of stroke, myocardial infraction, cardiovascular death and cardiac arrest was 19% less in succinobucol arm, when analyze with placebo and attained statistical significance [72].

Fasudil is a Rho-kinase inhibitor which is a crucial downstream effector of small GTP binding protein RhoA [73] and also determines that RhoA/Rho-kinase pathway plays a key role in

the pathogenesis of stroke, hypertension, heart-failure, vasospasm, ischemia reperfusion injury and atherosclerosis [74].

10. Anti-Hypertensive drugs:

Different aspects of hypertensive process could explain by various assumption of low grade inflammatory activation [75-77]. Therapeutic strategies contains the anti-inflammatory modulations of different hypotensive drugs and plays a protective role through reducing blood pressure or through some classes of drugs which have pleiotropic actions. [78,79]. In this situation, renin-angiotensin inhibitors system (renin inhibitors, angiotensin II receptor blockers, ACE: Angiotensin converting enzyme inhibitors) can be the perfect choice because of its crucial role for the activation of vascular inflammation is extensively established [80]. This is assured by various in vivo trial for reduction of different inflammatory markers which is induced by these types of drugs [81].

According to different hypertension guidelines, blood pressure are focused, which act as a major target for different therapeutic approach and proposed a combination drug,which boost the efficacy and reduce the side-effects. IVUS is a substudy of CAMELOT clinical trials which determines a particular reduction in the evolution of atheroma volume along a calcium antagonist such as amlodipine when compared to the ACE enzyme inhibitor (enalapril) [82].

11. Immunosuppressive agents: Immunosuppressive agents suppress the immune system and control lupus activity which affects majorly kidney, lungs, brain, and cardiovascular system. The methotrexate and canakinumab have been suggested as an effective choice.

Tumor necrosis factor- α (TNF- α) antagonists are largely used for the protection of cardiovascular disease and also in autoimmune disease [83]. In symptomatic patients, raise in TNF- α plasma levels for various ischemic cerebrovascular problems as compare to asymptomatic patients [84]. These drugs have anti-inflammatory effects which increase apolipoprotein (AI) and HDL cholesterol [85].

Interleukin-1 (IL-1) plays a key role in the inflammatory response that pursue in myocardial infraction (MI). Anakinra anatural antagonist, are used as a recombinant form and its safety and side-effects was executed on CRP serum levels and post myocardial infraction (MI) left ventricular remodeling [86]. This was capable to reduce left ventricular remodeling and differentiate CRP levels which interact with the modification in cardiac anatomy and it also assesses both echocardiography and cardiac magnetic resonance.

The mycophenolate mofetil drug (immunosuppressive drug) administered in atherosclerotic patients for defined time duration. These drugs constrict different biochemical and cellular inflammatory activation in the unsettled plaques of atherosclerotic patients and produce effects on both blood pressure and serum lipids [87,88].

There are some mechanisms of actions with different drug targets for atherosclerosis (Table-1). Please see appendix I for Clinical Trial and their result in brief.

References	Drug /Enzyme/ Receptor	Drug targets	Mechanism of action
Kristina et al. (1996)	Thiazolidinediones	PPARγ selective modulator	Decreases insulin resistance
Sagar et al. (2012)	Omega-3 fatty acids	PPARγ selective modulator	Anti-inflammatory effects in macrophage foam cells
Francisco and Carmelo (2012)	Endoglin	Endoglin receptor modulator	Reduces expression of inflammatory cell adhesion molecules
Petr et al. (2012, 2008)	Endoglin (CD 105, TGF-β receptor III)	Endoglin receptor modulator	Increases vascular smooth muscle cell Stabilize and reduce prothrombogenic state
John et al. (2010), Philip and John (2006), Sagar et al. (2012)	Niacin, Statin, Omega-3 fatty acids	CETP inhibitor	Increases HDL cholesterol levels, Reverses cholesterol transport system
Sagar et al. (2012)	Omega-3 fatty acids	ACAT enzyme inhibitor	Prevents transformation of macrophages into foam cells, Decreases synthesis of lipoproteins
Kathryn and Mason (2006), Kristina et al. (1996), Philip and John (2006), Sagar et al. (2012)	Scavenger Receptors, Thiazolidinediones, Omega-3 fatty acids	PPARα agonist	Decreases TG-rich lipoproteins, Increases HDL, Anti-inflammatory effects in vessel wall
Kathryn et al. (2001), Sagar et al. 2012	DGAT enzyme, Omega-3 fatty acids	DGAT enzyme inhibitor	Inhibit transfer of acyl group from acylcoenzyme-A to the sn-3 position of 1,2-diacylglycerol, Reduces triacylglycerol formation

Eugene et al. (2004), Jeffrey et al. (2001) Sagar et al. (2012)	3,5-diiodothyropropionic acid (DITPA), benzimidazole-based analogues of the potent MTP inhibitor BMS-201038, Omega-3 fatty acids	MTTP protein inhibitor	Prevents lipid assembly, transport, secretion of lipoproteins, triglyceride rich chylomicrons (in enterocytes) and VLDL, Modulates transportation of TG, cholesteryl ester, and phosphatidylcholine
Sagar et al. (2012), Tohru et al. 2002	Omega-3 fatty acids, YM-53601	Squalene synthase inhibitor	Prevent biosynthesis of the sterol nucleus of cholesterol
Eugene et al. (2004), Paul and Faith (2002), Sagar et al. (2012), Toshihiro (2010)	3,5-diiodothyropropionic acid (DITPA), Omega-3 fatty acids	Thyroid hormone analogues	Increases activity of lipoprotein lipase, Accelerates LDL-c clearance
Andrea et al. (2003), Sagar et al. 2012	2,3-oxidosqualene:lanosterol cyclase (OSC) enzyme, Omega-3 fatty acids	Lanosterol synthase inhibitor	Restrain four-ringed sterol intermediate formation, Prevent deposition of cholesterol within macrophages
Irina (2006), Sagar et al. (2012)	Cytochromes P450 (P450s); 7A1; 27A1; 11A1; 46A1, Omega-3 fatty acids	Cytochrome P450 modulator	Regulate conversion of cholesterol to 7ahydroxycholesterol
Bei et al. (2009), Sagar et al. 2012	Omega-3 fatty acids, AMPK, Thiazolidinediones, Metformin, Leptin	AMPK activator	Regulates glucose metabolism, Decreases hepatic lipogenesis, synthesis of new FA and cholesterol, Increases FA oxidation
Sagar et al. (2012), Vasilios et al. 2011	Omega-3 fatty acids, Statin, Statin-Niacin, Statin-Fibrate	Omega-3 FAs	Inhibit expression of SREBP-1, Reduces TG levels and atherogenic lipoproteins
Long et al. (2012)	Sera TC and LDL-C vaccine	Heat shock protein-65 and CETP vaccine	Reduction in immune tolerance against self antigen, Prevent transfer of CE into triglyceride-rich lipoproteins or LDL
Keith et al. (2010)	Varespladib	sPLA2 inhibitor	Prevents inflammatory, autoimmune and allergic
Keith et al. (2012), Pabloal and Juan (2006), Peter et al. (2008)	PAPP-A, Lp-PLA2, and Cystatin C, Endoglin	Lp-PLA2 inhibitor	Restrain formation of LysoPC and oxNEFA, Reduces proinflammatory and cytotoxic products
Agnes et al. (2005), Kathryn and Mason (2006)	Scavenger Receptors, oxidized LDL	Scavenger receptor inhibitor	Inhibits macrophage activation, lipid metabolism, and inflammation, Prevent induction of apoptosis, apoptotic cell clearance, and pathogen recognition

Table 1. Mechanism of action and their targets of drugs for atherosclerosis [89].

Conclusion

Inflammation plays a key role for the progression and development of atherosclerosis. They are mainly liable for stroke and heart disease or leads to death. Atherosclerosis can affects artery of any organ such as brain, heart, kidney, pelvis, legs, and arm. These conditions of atherosclerosis are responsible for development of subsequent disease such as coronary heart disease, carotid artery disease, and chronic kidney disease. These problems can be reduced by various anti-inflammatory approaches and these approaches have different types of drugs withindividual mechanism of action. The anti-inflammatory agents like statins (HMG-CoA Reductase Inhibitors), Niacin, flavonoids, and aspirin treats the atherosclerosis by lowering lipid levels from the body. Different clinical trials stated that these drugs have the lipid lowering properties and it decreases the chances of cardiovascular risk because of its anti-inflammatory actions. Aspirin performs as an anti-platelets as well as anti-inflammatory action that inactivate COX enzyme and suppresses the formation of prostaglandin and thromboxane. This review concluded the anti-inflammatory agents with their role in the treatment. There is a wide area for the research of impact of anti-inflammatory drugs or their role in the treatment of atherosclerosis or other cardiovascular diseases.

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Appendix: I

There are some information about the different clinical trials which consider in the review with names and its definitions.

Drugs Tested	Clinical Trial Name	Clinical Trial Acronym	No. of Patients/Duration/Method/Study	Result Outcome
Amlodipine, enalapril	Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis	CAMELOT	1328 patients, 24 months, double blinded, comparative study	Amlodipine produced normal blood pressure and reduced adversed cardiovascular events, but Enalapril produced smaller, non-significant treatment effects
Anacetrapib	Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib.	DEFINE	1632 patients, 24 months, Single blinded, comperative study	There was no change in the aldosterone, electrolyte, and blood pressure levels with Anacetrapib as compared to placebo
Atorvastatin	Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering	MIRACL	3086 adult patients, 16 weeks, double blind, comperative study	Atorvastatin reduces ischemic events in first 16 weeks as compared to placebo
Darapladib	Stabilization of Plaques Using Darapladib Thrombolysis in Myocardial Infarction 52	SOLID-TIMI 52	1326 patients, 30 days, double blind, comparative study	The primary end point was Myocardial infarction, myocardial ischemia, and coronary heart disease and it didn't reduce the risk of other major coronary events
Darapladib	Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy	STABILITY	15828 patients, 12 months, double blind, comparative study	Darapladib didn't reduce the risk of primary composite end point of myocardial infarction, stroke, and cardiovascular death

Ezetimibe, niacin	Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6 HDL and LDL Treatment Strategies in Atherosclerosis	ARBITER 6-HALTS	315 patients, 14 months, Comparative study	Niacin relapses carotid intima-media thickness (CIMT) and it is better than Ezetimibe for the patients who are taking statins
Multiple drugs	Atherosclerosis Risk in Communities	ARIC	15,792 patients, Repeated After 3-3 years (4 times)	Investigated hospitalized myocardial infarction and coronary heart disease in men and women with age 35-84 year and hospitalized stroke found in cohort patients
Nateglinide, valsartan	Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research	NAVIGATR	9031 patients, 6.5 year, placebo-controlled trial	After 6.5 year period of time, neither Nateglinide nor Valsartan improved the prognosis of cardiovascular events in these patients. Valsartan decreased the proportion of type-2 diabetes but Nateglinide didn't diminish the risk of diabetes
Niacin/laront	Treatment of High density lipoprotein to Reduce the Incidence of Vascular Events	HPS2-THRIVE	25,673 patients, 3.9 years, Comparative study	The addition of niacin-laropiprant to statin based LDL cholesterol lowering therapy didn't decrease the risk of cardiovascular events but nay increase the risk of adverse events
Olmesartan	Randomized Olmesartan and Diabetes Microalbuminuria Prevention	ROADMAP	4447 patients, 3.2 year, double blind, controlled trial	This drug was related with the delayed onset of microalbuminuria and the patients who are already suffering from coronary heart disease having higher rate of fatal cardiovascular events with Olmesartan
Pioglitazone	Prospective Pioglitazone Clinical Trial in Macrovascular Events	PROactive	5238 patients, 9.5 year, double blind, comparative study	Pioglitazone reduce macrovascular mortality and morbidity in the population of high risk patients
Pravastatin	Cholesterol and Recurrent Events	CARE	4159 patients, 5 year, double blind, comparative study	Study endpoints will be evaluated with predefined subgroups according to gender, age, and cardiovascular risk factor

Pravastatin, atorvastatin	Pravastatin or Atorvastatin Evaluation and Infection Therapy Thrombolysis in Myocardial Infarction 22	PROVE IT-TIMI 22	4159 patients, 5 year, double blind, comparative study	Pravastatin reduce the cardiovascular events in patients with a history of myocardial infarction
Pravastatin, atorvastatin	Reversing Atherosclerosis with Aggressive Lipid Lowering	REVERSAL	4159 patients, 5 year, double blind, comparative study	Study endpoints will be evaluated with predefined subgroups according to gender, age, and cardiovascular risk factor
Rosuvastatn	Justification for the Use of Statin in Prevention: an Intervention Trial Evaluating Rosuvastatin	JUPITER	17,802 patients, 1.9 year, double blind, placebo controlled study	The healthy person without hyperlipidemia but with important high sensetivity C-reactive protein level and Rosuvastatin reduce the cardiovascular events
Simvastatin	Aggrastat to Zocor	A-to-Z	4497 patients, 5 months, double blind, controlled study	Among patients with ACS, early initiation of Simvastatin resulted favorable in movement toward reduction of cardiovascular events.
Simvastatin, fenofibrate	Action to Control Cardiovascular Risk in Diabetes	ACCORD-Lipid	5518 patients, 4.7 year, double blind, comparative study	Fenofibrate cannot be added to statin for the treatment of lipid. when TG is >200 mg/dL and HDL is <35 mg/dL after statin therapy can be reduced LDL cholesterol level
Statins	Air Force/Texas Coronary Atherosclerosis Prevention Study	AFCAPS/TCAPS	6605 patients, 5.2 year, double blind, comparative study	Statin prevent coronary heart disease and well tolerated the risk of first acute coronary events without increasing the risk of either cancer or non-cardiovascular mortality
Succinobuol	Aggressive Reduction of Inflammation Stops Events	ARISE	6144 patients, 14-365 days, double blind, placebo controlled study	The high risk patients with ACS, the Succinobunol was not associated with aa difference in the primary endpoint of MI, CV death, Coronary heart disease compared with placebo
Torcetrapib	Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events	ILLUMINTE	15,067 patients, 1.52 year, double blind, comparative study	Torcetrapib could increased the risk of morbidity and mortility of unknown mechanism

Varepladib	Phospholipase Levels And Serological Markers of Atherosclerosis	PLASMA	135 patients, double blind, placebo controlled study	Varepladib is a effective anti-atherosclerosis agent because it reduces the atherogenic lipoprotein
Varespladib	Vascular Inflammation Suppression to Treat Acute Coronary Syndrome for 16 Weeks	VISTA-16	5145 patients, 16 weeks, double blind, randomized study	Patients with ACS, Varespladib didn't decrease the risk of cardiovascular events even increase the chances of MI

Table 2. clinical trials [90].