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Review Article

NATURAL PRODUCTS TARGETING ATHEROSCLEROSIS – AN EMERGING RISK FACTOR OF CARDIOVASCULAR DISEASES

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ABSTRACT

Cardiovascular disease is the leading cause of mortality in many economically developed nations accounting for about 30% of all deaths and its incidence is still increasing. Ongoing research aims to investigate and prevent the early development of cardiovascular risk factors such as atherosclerosis, hypertension, dyslipidemia, chronic inflammation, and insulin resistance. Atherosclerosis is a complex chronic disease characterized by the accumulation of lipids within arterial walls that eventually go on to form plaques, which can cause narrowing, hardening, and/or complete blockage of arteries. The development of the level of atherosclerosis from an early fatty streak lesion to a highly hazardous rupture-prone plaque is because of the many cellular and molecular events at each level hence, it is the inflammatory event. Statins are widely used as the clinical treatment for atherosclerosis due to its excellent efficacy in reducing the low-density lipoprotein (LDL) level. Statins competitively inhibit the HMG-CoA reductase enzyme that plays a great role in catalyzing the rate-limiting step in the biosynthesis of cholesterol. The increase in hepatic LDL receptors' expression is triggered by the reduction of hepatocyte cholesterol concentration and helps to clear LDL from the circulation. However, the consumption of statins causes adverse health effects such as liver injury and muscle toxicity. The other side effects include myopathy, rhabdomyolysis, and acute renal failure. Epidemiological studies have shown that the risk of heart diseases can be reduced through the consumption of flavonoid rich diets. The beneficial effects of n-3 polyunsaturated fatty acids (n-3 PUFAs) were also proved in several observational and experimental studies. Understanding the role of the immune system in atherosclerosis provides an impetus for development and testing of strategies that modulate the immune system to reduce atherosclerosis. Thus, attention is now directed to the natural products from plant origin that possess antiatherosclerotic activity and can promote human health.

Key words: Cardiovascular disease, Atherosclerosis, LDL, Flavonoids, Natural Products.

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INTRODUCTION

Being a chronic inflammatory disease, atherosclerosis is becoming the leading cause of death in many of the developed countries (Margaret, 2010).

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Cardiovascular diseases (CVDs) like myocardial infarction (heart attack), acute coronary syndrome, or stroke arise through the development of plaques and lesions inside the arteries (Navab *et al*., 1996; Ross, 1999; Steinberg and Witztum, 1999; Keaney, 2000). Hypercholesterolemia, hypertension, and obesity give high risks for the progression of CVDs. The development of the level of atherosclerosis from an early fatty streak lesion to a highly hazardous rupture-prone plaque is because of the many cellular and molecular events at each level hence, it is the inflammatory event (Robert, 2005). These fatty streaks are one of the signs of atherosclerosis, which is first observed by Russell Holman and this fatty streak develops,

thrombosis or hemorrhage (Brian *et al*., 2012). A persistent increase in circulating low-density lipoprotein (LDL) levels in the body is one of the most important causes for the initiation and progression of atherosclerosis. In this respect, macrophages play important role by increasing accumulation of lipids in blood vessels, leading to inflammation and plaque formation. Two different theories proposed, describe the events involved in atherogenesis. The first hypothesis is ''response to injury,'' in which endothelial lining's injury initiates events of deposition of LDL in the intimal space, followed by recruitments and migration of monocyte-derived macrophages, which take up modified LDL and become foam cells (John, 2000; Ross, 1993; Ross *et al*., 1977). The second is ''response to retention''; LDL is deposited in the intimal space and undergoes modification. Modified LDL serves as a chemoattractant for monocytes and macrophages. Macrophages remove modified LDL via scavenger receptors and become foamy (Williams and Tabas, 1995). LDL accumulates within the intimal space and subsequently undergoes modification such as oxidation, converting LDL into oxidized LDL, which acts as a major immunogen (Wilensky and Hamamdzic, 2007). Oxidation of LDL in the intimal space is not known exactly; however, lipoxygenases, myeloperoxidase, inducible nitric oxide synthase and NADPH oxidases have LDL oxidation capacity (Li and Glass, 2002). The activated endothelial cells (EC) enhance the expression of adhesion molecules, such as intracellular adhesion molecule, vascular cell adhesion molecule, E- and P-selectin. Adhesion molecules have a major role in monocyte recruitment on the arterial endothelium. P-selectin binds to Pselectin glycoprotein ligand-1, which is present on monocytes (John, 2005; Elstad *et al*., 1995). P-selectin glycoprotein ligand-1 allows the capturing, rolling and activation of monocytes (Weyrich *et al*., 1995). P and E-selectin has similar functions in the progression of atherosclerosis (Chandak *et al*., 2011). VCAM-1 is another important molecule in monocyte recruitment and firm adhesion to the endothelial surface. Very late antigen-4 expressed by monocytes is a ligand for vascular cell adhesion molecule -1. Intracellular adhesion molecule has a role in monocyte adhesion, spreading and migration into the sub-endothelial space. Monocytes enter the endothelial space and differentiate into macrophages by macrophage colony-stimulating factor secreted by EC and smooth muscle cells (SMCs). Activated macrophages in the sub-endothelial space secrete macrophage-chemoattractant protein-1. EC induces the expression of macrophage-chemoattractant protein-1 in the presence of oxidized phospholipids, which are components of oxidized LDL (Li and Glass, 2002). Macrophages remove modified LDL via scavenger receptor A, scavenger receptor B1 and cluster of differentiation. After internalization, endosomes are transferring LDL to lysosomes. After lysosomal degradation of LDL, free cholesterol is produced, which is re-esterified into cholesteryl esters via acyl-CoA: cholesterol acyltransferase1 (ACAT1). Accumulation of lipid-laden macrophages (foam cells) in the arterial wall is the hallmark of atherosclerosis. The atherosclerosis is the major complication of diabetes mellitus because many studies found that the diabetic patients have 2–5 times the death rate than non-diabetic patients (Gerrity and Antonoy, 1997). The progression of atherosclerosis is characterized by development of plaque on the insides of arteries, which later hardens and narrows the arteries, leads to reduced supply of oxygen rich blood to organs and other parts of the body. This can lead to various serious cardiovascular complications like heart attack, stroke, or even death (Paolo *et al*., 1995). Fig. 1 shows the development of atherosclerotic-plaque in the coronary artery. Management of adverse cardiovascular outcomes of atherosclerosis through risk factor identification and modification has been an active area of research over the past few decades. As a result, several large scale randomized clinical trials and observational studies have shown intensive risk reduction therapy to be very effective and critical in reducing adverse cardiovascular outcomes in patients with atherosclerosis (Mervi *et al*., 2012).

Retention of intracellular lipids or lipidosis that is the accumulation of cholesterol and other lipids in the arterial cells is the most prominent manifestation of atherosclerosis at the arterial cell level. Williams and Tabas (Williams and Tabas, 1995; Williams and Tabas, 1998) proposed the Response-to-Retention model of atherogenesis. Although atherosclerosis is a complex and multifactorial process, the key initiating process in atherogenesis is the retention of sub endothelial cholesterol that is necessary to provoke lesion initiation. Retention of cholesterol transported by low density lipoprotien (LDL) in sub endothelial space of arterial wall is an absolute requirement for lesion development. According to Tabas *et al*. (Tabas *et al*., 2007) the molecular basis of lipoprotein retention is associated with interaction of lipoprotein and extracellular matrix molecules. Local responses to these retained lipoproteins include inflammatory response with subsequent lesion development (Insull, 2009). Specific focus is placed on the potential of these innate immune targets for therapeutic interventions to retard the progression of atherosclerosis or to induce its regression (Moore and Freeman, 2008). The response-to-retention model considers only the retention of cholesterol on extracellular matrix, while completely ignoring the retention of intracellular cholesterol. Intracellular cholesterol retention is accompanied by increased proliferative activity of vascular cells and increased synthesis of extracellular matrix (Orekhov *et al*., 1990; Orekhov *et al*., 1988). Along with the retention of intracellular cholesterol, both proliferation and fibrosis are characteristic features of atherosclerosis at the arterial cell level, too. Thus, intracellular cholesterol retention may be the initial event of all major manifestations of

atherosclerosis on cellular level. Intracellular cholesterol retention may be regarded as a novel target for anti-atherosclerotic therapy. This allows us to consider cellular retention of cholesterol as a novel target for anti-atherosclerotic therapy. In this case the target is not the level of blood cholesterol but the level of cholesterol in vascular cells. Statins are widely used in the treatment of atherosclerosis due to its excellent efficacy in reducing the low-density lipoprotein (LDL) level (Gould *et al*., 1998; Ray and Cannon, 2005). Statins competitively inhibit the enzyme, HMG-CoA reductase that plays a great role in catalyzing the rate-limiting step in the biosynthesis of cholesterol (Endo, 1977). The raise in hepatic LDL receptors' expression is triggered by the reduction of hepatocyte cholesterol concentration and helps to clear LDL from the circulation (Brown and Goldstein,1986; Maron *et al*., 2003). However, the consumption of statins causes adverse effects such as liver injury and muscle toxicity (Maron *et al*., 2003; Bradford *et al*., 1991). The other side effects include myopathy, rhabdomyolysis, and acute renal failure (Pierce *et al*., 1990). Hence, now attention is directed to the natural products from plant origin that possess antiatherosclerotic activity and can promote human health. This can eventually reduce possible health effects due to the long period consumption of statins. Many researches on bioactive compounds and their possible medicinal attributes have been studied during the past decades (Agarwal and Rao, 1998; Auger *et al*., 2005; Loke *et al*., 2010). Plant and plant by-products can be used for isolating health promoting bioactive compounds since there are substantial plant sources which are relatively inexpensive. The bioactive compound from plant extracts has shown many health promoting effects in both *in vitro* and *in vivo* studies, such as antioxidant (Skerget *et al*., 2005; Sultana and Anwar, 2008), hypoglycemic (Ribnicky *et al*., 2009; Patil *et al*., 2011; Wainstein *et al*., 2012), hypotensive (Tabassum and Ahmad 2011), and hypocholesterolemic (Koo and Noh 2007; Singh *et al*., 2009; Ismail *et al*., 2010) effects. The aim of this review is to focus on various natural products that can target atherosclerosis and can alleviate it with comparatively less adverse effects.

Natural Products

Atherosclerosis develops over many years, so the anti-atherosclerotic therapy should be long term or even lifelong. Tachyphylaxis, long-term toxicity and cost amongst other issues may present problems for the use of conventional medications in the long-term. Drugs based on natural products can be a good alternative. *Ex vivo* cellular model can be used to test natural products. Prevention of intracellular cholesterol retention caused by certain mushroom species and sea products has been investigated. Extracts from 20 Korean mushroom species exhibit intracellular cholesterol retention revealed by cell culture test (Li *et al*., 1989). Among sea products, mollusk and krill meat were investigated. Two hours after a single dietary load with canned meat of a mollusk belonging to the genus Buccinum, the patient's blood serum acquired marked anti-atherosclerotic properties. Incubation of this serum with cultured atherosclerotic cells led to a fall in intracellular cholesterol retention. Patients of another group received a single dietary dose of Antarctic krill meat. Two hours later, the retention of cellular cholesterol induced by blood sera decreased, and four hours later, it was practically absent (Orekhov 2013).

To develop a dietary therapy based on the krill meat, the effective dose and proper regimen have been established. The antiatherosclerotic activity of krill meat was evaluated by the ability to reduce intracellular cholesterol retention. The dose-effect dependence was revealed by comparing the efficacy of the two doses, and found that krill meat possesses anti-atherosclerotic effects at a dose of 10-20 g, half-maximum effect was reached at a dose of 30 g, and the maximum effect was achieved at a dose of 50 g. This approach will be useful in the development and optimization of anti-atherosclerotic dietary therapies. Numerous extracts of natural products revealed their effects on their capacity to prevent intracellular cholesterol retention caused by atherogenic blood sera from atherosclerotic patients have also been tested. Naturally, the tested agents included anti-atherosclerotic, pro-atherogenic, and neutral products. Among the anti-atherosclerotic natural products, the most effective was garlic. The *in vitro* effect of garlic extract on intracellular cholesterol retention was investigated. Garlic prevented the serum-induced accumulation of free cholesterol and reduced the accumulation of cholesteryl esters. The effect of garlic on cholesteryl esters may be explained by the action on enzymes responsible for cholesteryl ester metabolism. The study has shown that garlic inhibits acyl-CoA: cholesterol acyltransferase, which participates in cholesteryl ester formation, and stimulates cholesteryl ester hydrolase, which degrades cholesteryl esters (Orekhov and Tertov, 1997).

Further investigations *ex vivo* confirmed the *in vitro* effects of garlic (Orekhov and Grunwald, 1997). In *ex vivo* experiments dry garlic powder was applied. Using *ex vivo* model the effective dose of oral garlic powder administration was optimized. The anti-atherosclerotic activity of garlic powder was evaluated by the ability to reduce intracellular cholesterol retention.

The dose-effect dependence was revealed by comparing the efficacy of the two doses, and it was found that garlic powder possesses antiatherosclerotic effects at a dose of 50-300 mg. The minimum dose causing maximum effect was 150 mg. Using the optimal dose of 150 mg garlic powder the study has showed that long-term treatment for months and years leads to a significant reduction of intracellular cholesterol retention or its extinction (Orekhov and Grunwald, 1997; Orekhov *et al*., 2013). These data stimulated us to develop a drug based on

garlic powder and carried out a clinical study of the effects of this drug on atherosclerosis regression.

The study has developed the time-released garlic powder tablets referred to as Allicor that have been registered and are now being manufactured by INAT-Farma, Ltd. (Russia). The AMAR study (Atherosclerosis Monitoring and Atherogenicity Reduction) was carried out to estimate the effect of two-year treatment with Allicor on the progression of carotid atherosclerosis in asymptomatic men in a double-blinded, placebo controlled randomized clinical trial (ClinicalTrials.gov Identifier, NCT01734707). The primary outcome was the rate of atherosclerosis progression, measured by high-resolution B-mode ultrasonography as the increase in carotid intima-media thickness (CIMT) of the far wall of common carotid arteries (Orekhov *et al*., 2013).

Effects of Allicor promoted new clinical trials of two other drugs based on natural products, Inflaminat, which possesses anti-cytokine activity, and the phytoestrogen-rich drug Karinat, which is designed for postmenopausal women. Inflammatory cytokines play significant role at every stage of atherogenesis (Libby, 2006; Aidinian *et al*., 2006; Daugherty *et al*., 2005). So, anti-cytokine drugs may be effective for the prevention of atherosclerosis. A drug Inflaminat was developed, which is based on calendula, elder and violet. The laboratory investigations demonstrated that Inflaminat suppresses secretion of pro inflammatory cytokines and reduces intracellular cholesterol retention. A pilot study (Clinical Trials.gov Identifier, NCT01743404) was carried out with Inflaminat using a protocol like that of the AMAR study. New study demonstrated atherosclerosis regression effects of Inflaminat and a statistically significant difference from the baseline as well as from placebo group in asymptomatic men (Orekhov *et al*., 2013).

Flavonoids represent a broad family of more than 4000 secondary plant metabolites. The four predominant classes are 4-oxoflavonoids (flavones and flavonols), isoflavones, anthocyanins, and flavan-3-ol derivatives (tannins and catechin) (Rhodes and K. R. Price 1996; Dinelli *et al*., 2006; Rocha-Guzm'an *et al*., 2007). For centuries, preparations that contain flavonoids are applied as the primary physiologically active components that have been used for treating human diseases (Havsteen, 1983). Epidemiological studies have shown that the risk of heart diseases can be reduced through the consumption of flavonoid rich diets [Hertog *et al*., 1995]. Flavonoids may inhibit the vascular diseases' development through alteration in endothelial cell eicosanoid production (Schrammand and German, 1988). Flavonoids also showed blood pressure lowering effect in hypertensive and normotensive subjects while flavonoids may have beneficial actions in obesity due to their capacity to regulate fatty oxidation and improve adipocyte functionality (Galleano, 2012). Besides, food derived flavonols (quercetin, kaempferol, and myricetin) have been reported to exhibit various biological functions and medicinal properties such as antioxidant, antithrombotic, anti-inflammatory, anti-atherogenic, antiatherosclerotic, and cardioprotective effects (Vinson *et al*., 1995; Hollman *et al*., 1997; Manach *et al*., 2005; Kleemann *et al*., 2011). The plants like *Garcinia cambogia* (Koshy *et al*., 2001), *Mangifera indica* (Anila and Vijayalakshmi, 2003), *Hypericum perforatum* L (Zou *et al*., 2005), and *Asparagus racemosus* (Visavadiya and Narasimhacharya 2009) that contain flavonoids have been proven to significantly lower the risk of atherosclerosis and CVD. Recent studies demonstrated that catechin and quercetin (two major honey flavonoids) (Figure 2) (Khalil and Sulaiman, 2010; Afroz *et al*., 2015) consumption exhibited inhibitory effect on development of aortic atherosclerotic lesions and on atherogenic modification of LDLs (Hayek *et al*., 1997). The honey-derived flavonoid naringin inhibits hypercholesterolemia-induced intercellular adhesion molecule-1 (ICAM-1) expression on endothelial cells. Naringenin decreases LDL and triglycerides levels as well as inhibiting glucose uptake, increase high density lipoproteins (HDLs), co-oxidation of NADH, suppression of protein oxidation, suppression macrophage inflammation, inhibits leukotriene B4 leading to reduced monocyte adhesion and foam cell formation and the down-regulate genes related to atherosclerosis (Choe *et al*., 2001). Apigenin, commonly found in honey, improves various parameters of cardiovascular disease, stimulates the favourable aspects of the immune system and inhibits platelet aggregation (Orhan *et al*., 2015).

Polyunsaturated Fatty Acids (PUFAs)

The beneficial effects of n-3 polyunsaturated fatty acids (n-3 PUFAs) were proved in several observational and experimental studies. The lipid lowering action of n3-PUFAs was detected at the beginning, so these nutrients were used for the treatment of dyslipidemic disorders. Their anti-inflammatory, antithrombotic, antiatherosclerotic, and antiarrhythmogenic effects were observed later. Low-grade chronic inflammation is now recognized as a prominent process in the development of atherosclerosis and coronary heart disease. The induction of inflammation may well provide a link between hyperlipidemia and atherogenesis (Dei Cas *et al*., 2007; Ross, 1999). Atherosclerosis is now considered a "systemic disease" featured by low-grade arterial inflammatory lesions that can develop through the disease progression (Montecucco and Mach 2009). In physiological conditions, endothelial cells synthesize and release adequate amounts of nitric oxide (NO) and prostaglandins (such as PGE2 and PGE3) and maintain a downstream balance between pro- and anti-inflammatory molecules. However, in the presence of atherosclerosis this balance disrupts leading towards an increase production of proinflammatory cytokines as interleukins 1, 2, and 6 (IL-1, 2, and 6) and tumor necrosis factor α (TNF-α), with

further progression of the disease (Das, 2007). These pro-inflammatory cytokines can induce oxidative stress by enhancing the production of reactive oxygen species (ROS) by monocytes, macrophages, and leukocytes. PUFAs and their eicosanoid derivatives may play a significant role modulating the inflammatory response (Das, 2006).

Metabolism of PUFAs

Unsaturated fatty acids are referred to as PUFAs when two or more double bounds are present. There are two PUFAs families, omega-3 (n-3) and omega-6 (n-6) fatty acids. They differ in location of the last double bond relative to the terminal methyl end of the molecule. The human body can produce almost all fatty acids, except linoleic acid (LA, C18:2 n-6, precursor to the n-6 series of fatty acids) and α-linoleic acid (ALA, C18:3n-3, precursor to the n-3 series of fatty acids). These two PUFAs are named "essential fatty acids" because the body cannot synthesize them (Patterson *et al*., 2012). Endogenous conversion (elongation and desaturation) of the initial C18 PUFA precursors results in the synthesis of longer-chain counterparts such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the n-3 family and dihomo-γ-linoleic acid (DGLA) and arachidonic acid (AA) in the n-6 family (Abeywardena and Patten, 2011). In humans, the biochemical pathways converting ALA to EPA and EPA to DHA are limited: 0.2–8% of ALA is converted to EPA (generally more in women) and 0–4% of ALA to DHA (Burdge, 2004; Burdge *et al*., 2003; Burdge *et al*., 2002; Emken *et al*., 1994; Pawlosky *et al*., 2001). Results from pilot studies suggest that ALA conversion is also limited to function as a surrogate for fish consumption (Goyens *et al*., 2005). Thus, tissue and circulating EPA and DHA levels are primarily related to their dietary intake. Fish is the major food source of long-chain n-3 PUFAs, including EPA, DHA, and docosapentaenoic acid (DPA), while ALA is a plant n-3 fatty acid mainly found in seeds, nuts, and their oils. Thus, plant sources of n-3 fatty acids cannot currently be considered as a replacement for seafood-derived n-3 PUFAs. This suggests that n-3 fatty acids derived from different sources might have their own specific effects on cardiovascular risk markers. Linoleic acid is thought to decrease the conversion of ALA into EPA and DHA by competing for the n-6-desaturase enzyme (Harper *et al*., 2007). Previous studies showed that genetic variations in this enzyme may be related to cardiovascular disease (Truong *et al*., 2009). Furthermore, because the two fatty acid pathways are mutually exclusive (i.e., n- 3 fatty acid cannot become n-6 fatty acid and vice versa), a balanced intake of ALA and LA as precursors or of their longer-chain products EPA, DHA, and AA is required (Abeywardena and Patten 2011).

PUFAs and Cardiovascular Disease

There is a vast amount of epidemiologic evidence of a cardioprotective effect of fish oil-derived EPA and DHA and it was confirmed in randomized controlled trials [Hansen and Harris 2007; Harris *et al*., 2008; Mozaffarian, 2005; Harris *et al*., 2008). Several intervention studies have shown that an increased intake of eicosapentaenoic acid (EPA, C20:5n-3) and docosahexaenoic acid (DHA, C22:6n-3) lowers the risk of coronary heart disease (CHD) (Lemaitre *et al*., 2003). The first GISSI-Prevenzione trial, a randomized open label study in 11324 Italian patients with recent myocardial infarction, demonstrated that patients had a 15% lower combined risk of mortality, nonfatal myocardial infarction, and stroke upon supplementation for 3.5 years with 850mg·day-1 of LC n-3 PUFA. The relative risk of cardiovascular mortality was also decreased by 30% and that of sudden death by 45%. The GISSI-Prevenzione trial demonstrated that a significant protective effect could be obtained with doses much lower than those previously considered necessary for significant beneficial effects. The second GISSI-HF study, a randomized double-blind placebo-controlled trial in 6975 Italian patients with chronic heart failure, revealed a moderate decrease in both all-cause mortality admissions to hospital for cardiovascular disease upon supplementation for an average of 3.9 years with 1 g of LC n-3 PUFA daily. Again, the beneficial effects were seen in a population already treated with recommended therapies. The "Japan Eicosapentaenoic acid (EPA) Lipid Intervention Study," (JELIS) trial, was performed on 18645 Japanese men and women with hypercholesterolaemia treated with statins. Supplementation with 1.8 g EPA daily decreased major coronary events by 19% over 4.6 years. Non-fatal coronary events, rather than CHD death, were decreased (Yokoyama *et al*., 2007). A large amount of investigations suggests, the cardioprotective effects of LC n-3 PUFAs EPA and DHA intake in human subjects, because of their lipid lowering, hypotensive, antiarrhythmic, and anti-thrombotic properties. Moreover, studies performed in the last twenty years showed heterogeneous effects of different n-3 PUFAs on various cardiovascular outcomes, which may be of paramount relevance in primary and secondary prevention of cardiovascular disease. Recent in vitro investigations as well as clinical studies also demonstrated that LC-n3-PUFAs significantly interact with inflammation-related mechanisms, such as endothelial activation, modification of eicosanoid metabolism, and resolution of the inflammatory process. Low-grade chronic inflammation is present in several diseases and is characterized by abnormal circulating levels of pro- and anti-inflammatory cytokines. N-3 PUFAs may modulate inflammation, that is, suggested by the reduction of plasma inflammatory cytokines (TNF-α, Il-6) and inflammatory markers as high sensitive C reactive protein, observed after the intake of EPA and DHA. Low-grade chronic inflammation plays a key role in the induction and progression of atherosclerosis and consequently of cardiovascular disease. Taking into consideration the pleiotropic nature of their actions, it is suggested that

dietary intake of LC n-3 PUFAs may lead to improvements in cardio-metabolic health parameters of their antioxidant, anti-inflammatory, and antiarrhythmic actions.

Enzymatic Targets in Atherosclerosis:

Many enzymes are associated with atherosclerosis, either in the main stream of lipid biosynthesis and transport or in the collateral and intertwined pathways of oxidative stress, inflammation, vascular remodelling or chromatin stability and are therefore revised herein. Enzyme exploration led to important developments. At the beginning, there were the statins, derived as inhibitors of hydroxy-methyl-glutaryl CoA (HMG-CoA) reductase, currently used widely to decrease lipid levels. At the other end, the inhibitors of the recently discovered proprotein convertase subtilisin/kexin type 9 (PCSK9) are awaiting the validation in clinical trials with great hopes for the future. In between, one can find some palliatives, as aspirin, an inhibitor of cyclooxygenase (COX), but also many invalidated candidates. Classical pharmacological data and newer approaches, like genetic knockouts in murine atherosclerosis models, are reviewed to appreciate the involvement of an enzyme in atherogenesis (Figure 3). However, the pursuit of an efficacious drug has been long and, in many cases, disappointing. Conclusions can be drawn from the overview of both successes and failures, in a quest for the best (Fuior *et al*., 2015).

Immunomodulation for Atherosclerosis

Understanding the role of the immune system in atherosclerosis provides an impetus for development and testing of strategies that modulate the immune system to reduce atherosclerosis. Several immunomodulating strategies are being evaluated to influence atherosclerotic vascular disease (Table 1) (Prediman *et al*., 2004).

Where, CETP, cholesterol ester transfer protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Major targets for anti-atherosclerotic activity

i. Modification of lipoprotein levels

Lipoproteins are composed of lipids (phospholipids and triacylglycerol), proteins and cholesterol. It is well recognized that eminent blood lipid levels amount to the primary risk factor for atherosclerosis. Epidemiological studies have indicated that dyslipidemia and coagulation disturbances are among most considerable risk factors of the development of atherosclerotic conditions (Erqou *et al*., 2009; Nordestgaard *et al*., 2010). In state of hyperlipidemia, excess of LDL infiltrates arteries and is retained in the tunica intima. The retained LDL undergoes oxidative modifications in the sub-endothelial space (Leitinger, 2003; Skalen *et al*., 2002). The infiltration of LDL can be controlled either by direct lowering of lipoprotein levels of the blood or by elevating levels of HDL or by targeting lipid lowering enzyme i.e. HMG CoA reductase enzyme. Based upon these observations, it was found that ethanolic extract of *Apium graveolens* seeds (Kamal *et al*., 2009) significantly attenuated atherosclerosis by decreasing serum total cholesterol (TC), triglyceride (TG), phospholipids, LDL, and VLDL. Moreover, the ethanolic extract of *Passiflora foetida* at doses of 100, 250 and 500 mg/kg was found to lower the levels of TC, TG, LDL and VLDL significantly (Ravi *et al*., 2016). The role of HDL in removal of excess of cholesterol from cells by reverse cholesterol transport is well renowned. The multistep process of reverse cholesterol transport results in the movement of cholesterol from peripheral tissues back to the liver via plasma. Thus, elevation of HDL would be beneficial for attenuation of LDL infiltration (Olga and Yechezkiel, 1999). Ethanolic extract of bark of *Terminalia arjuna* at a dose of 100 and 200 mg/kg (p.o) significantly elevated HDL and induced partial inhibition of aortic atherosclerosis (Saravanan *et al*.,2011). Aqueous and ethanolic extracts of leaves of *Cassia auriculata* have also augmented the HDL levels (Shipra *et al*., 2009). Ethanolic extracts of *Cinnamomum zeylanicum* bark and *Syzygium cumini* seeds at a dose of 200 mg/kg (p.o) have significantly increased the HDL level and decreased TC, TG and LDL levels as well (Khaled and Moattar, 2015). HMG CoA reductase is known to catalyze the conversion of the HMG CoA to mevalonate. Methanolic extract of fruits of *Emblica officinalis* at a dose of 10 and 20 mg/kg reversed the atheromatous plaques by inhibition of HMG CoA reductase activity (Antony *et al*., 2006). Ethanolic extract of *Lagenaria siceraria* at a dose of 200 and 400 mg/kg (p.o) ameliorated the atheromatous lesions by modulating HMG-CoA reductase and lipoprotein lipase enzyme activities (Mithun *et al*., 2014). Methanolic extract of *Ficus virens* bark at a higher dose of 100 mg/kg (p.o) altered the levels of lipoproteins, oxidative stress and inhibition of hepatic HMG-CoA reductase activity as well (Danish *et al*., 2015).

ii. LDL oxidation

Oxidative damage by free radicals has been concerned as the ground of diverse diseases. Numerous evidence from the conducted studies put forward that oxidation of LDL plays a key role in pathogenesis of atherosclerosis (Anna *et al*., 2013). After infiltration of LDL in the artery, LDL is converted to mmLDL in which LDL can still be recognized by the LDL receptors. The monocytes are attached to endothelial cells that have been induced to express cell adhesion molecules by mmLDL. Further, mmLDL undergoes oxidation, which leads to formation of extensively oxidized LDL (oxLDL). Oxidation of LDL involves lipid peroxidation, in which the polyunsaturated fatty acids in LDL core and in phospholipids are swiftly converted to lipid hydro peroxides and aldehydic lipid peroxidation products. The so-formed particles do not bind to LDL receptor but rather

bind to scavenger receptors expressed on macrophages and smooth muscle cells (Christopher and Joseph, 2001; Leitinger, 2003; Nakashima *et al*., 1998; Skalen *et al*., 2002). Fortification against LDL oxidation is a goal study for prevention of the instigation and progression of atherosclerosis. Antioxidants, which can efficiently hold back the LDL oxidation, may prevent atherosclerosis due to the early diminution of atherosclerotic progression. Methanolic extract of fruits of *E. officinalis* at a dose of 10 and 20 mg/kg (p.o) impede the generation of atheromatous plaques by prevention of LDL oxidation (Antony *et al*., 2006). Rhizomes of *Zingiber officinale roscoe* attenuated the development of atherosclerotic lesions via reduction in plasma and LDL cholesterol levels and a significant reduction in the LDL basal oxidative state, as well as their susceptibility to oxidation and aggregation (Fuhrman *et al*., 2000). Hydro alcoholic extract of rhizomes of *Curcuma longa* has reduced the oxidative stress and attenuation of the development of fatty streaks (Quiles *et al*., 2002). Ethanolic extract of flowers of *C. auriculata* also produced protective effect against atherosclerosis by exhibiting strong antioxidant activity (Vijayaraj *et al*., 2011). Methanolic extract of *Aframomum melegueta* seeds has elevated the antioxidant enzyme levels at 100, 200 and 400 mg/kg dose in albino Wistar rats (Samuel *et al*., 2014). Kim *et al*. (2015) have found the extract of *Scutellariae baicalensis* effective against inhibition of LDL oxidation and thus possessing an anti-atherosclerotic potential. Ethanolic extracts of *C. zeylanicum* bark and *S. cumini* seeds at a dose of 200 mg/kg (p.o) have elevated the levels of antioxidant enzyme, showing inhibitory potential of plants against LDL oxidation (Khaled and Moattar, 2015). Hydro-alcohol extract of *Myrtus communis* was studied for its inhibitory activity against production of ox-LDL, which leads to a decrease in the development and the progression of atherosclerosis (Bahador *et al*., 2015).

iv. Endothelial cell dysfunction and adhesion of molecules

Endothelial cells are an edge and functional link between circulating blood and the rest of the blood vessel wall. Endothelium produces NO, prostacyclin, endothelin-1 and angiotensin II (Ignarro *et al*., 1999; Vallance and Chan, 2001). NO which is an important signalling molecule, synthesized by nitric oxide synthase (NOS) enzymes family, has a crucial role in vascular homeostasis. NO exhibits multiple effects on the vessel wall including activation and aggregation inhibition of platelets, inhibition of cell adhesion and migration, relaxation and inhibition of proliferation of vascular smooth muscle cells etc. Any biochemical or physical damage in the phenotype of endothelial cells leads to impaired production of homeostatic mediators of vascular health i.e., NO which results to progression of atherosclerosis (Claudio *et al*., 2007; Vallance and Chan, 2001). Thus, sound levels of NO and endothelial cell functioning can help in preventing the development and progression of atherosclerosis. Fruits of *Gardenia jasminoides* have shown restoration of endothelium-dependent relaxation increasing the vessel eNOS activity, leading to elevation of NO production (Tang *et al*., 2006). Leaves of *Camellia sinensis* have shown a decrease in atherosclerosis progression by reversing endothelial dysfunction (Minatti *et al*., 2012).

Figure 1. Shows the atherosclerosis-plaque develops in the coronary arteries.

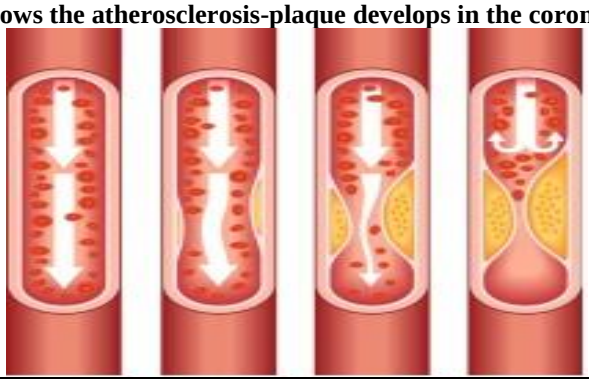

Figure 2. Potential anti-atherosclerotic effects of honey-derived flavonoids.

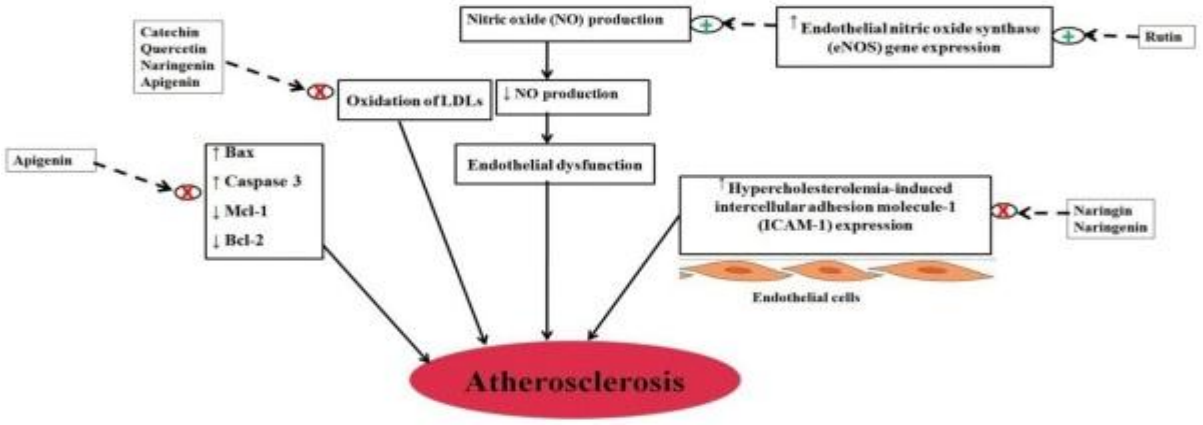

Figure 3. Schematic representation of the main enzymes used as targets for atherosclerosis, grouped by their metabolic action. The inhibition or gene knockout of the enzymes written in red protects to atherogenesis; for the enzymes written in green, the overexpression has an athero-protective effect and their inhibition aggravate the atheromatous process.

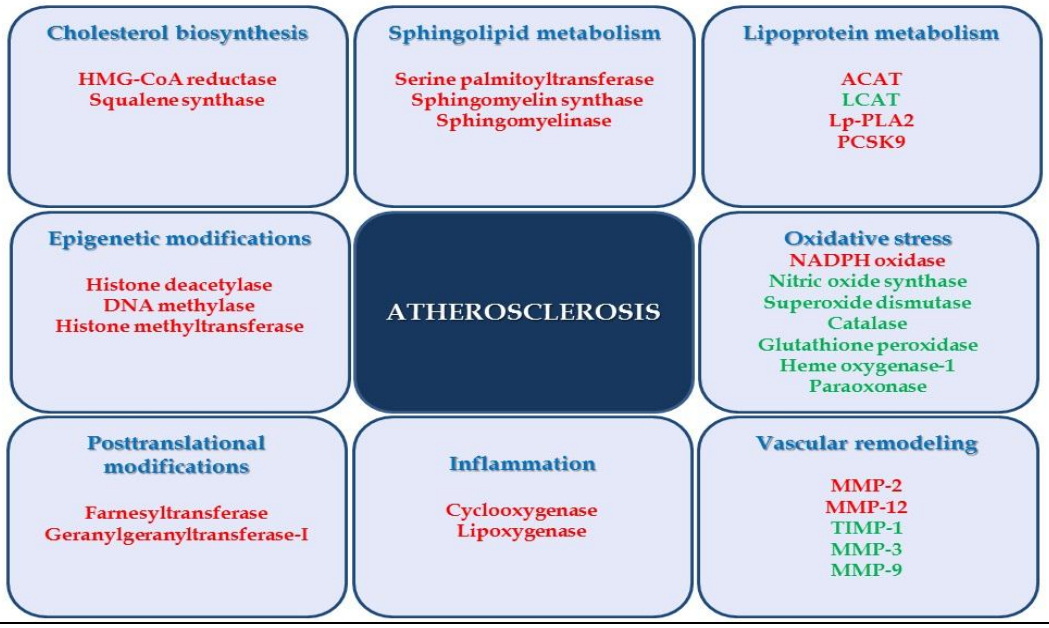

Table 1.Immunomodulation Strategies for Atherosclerosis

Immunosuppressive therapy Corticosteroids Cyclosporine Sirolimus
Immunization (vaccination) **Active** 1) native LDL, oxidized LDL, apoB-related peptides, phosphorylcholine as antigens 2) influenza and pneumococcal vaccines 3) CETP vaccine to raise HDL levels **Passive** Immunoglobulin (IgG), antibody to oxidized LDL/apoB-related antigens
Tolerization Mucosal exposure to heat-shock protein

v. Inflammatory process and smooth muscle cell migration and plaque formation

In atherosclerosis, there is an abnormal activation of inflammatory cells, which are aimed toward the lipid deposited in the vascular wall. The inflammatory process in the atherosclerotic artery leads to increased blood levels of inflammatory cytokines and other acute-phase reactants. Specifically, there is an increase in plasma levels of pro-inflammatory mediators like cytokines, chemokines and migratory potential in macrophages (Croce and Libby, 2007). T-helper cells (Th) and regulatory T-cells predominate in atherosclerosis. During early atherosclerosis, the Th cells secrete many inflammatory pro-atherogenic cytokines like interferon-g. Interactions between macrophage foam cells, Th1 and Th2 cells establish a chronic inflammatory process, which results in attraction and migration of SMCs. SMCs further proliferate and thicken the arterial wall (Mallat *et al*., 2009). The therapeutic agents with anti-inflammatory response may alter this step and help in attenuating the progression of atherosclerotic plaque formation. Methanolic extract of *Ruta graveolens* L. was investigated for anti-inflammatory effect on murine macrophage cells (J-774). Results revealed that plant extract has shown significant inhibitory effects on upregulation iNOS and COX-2 enzymes which leads to production of pro-inflammatory mediators (Raghav *et al*., 2006). The primary function of SMCs is to create vessel contraction in the presence of an external stimulus. During atherosclerosis, SMCs are activated, which leads to their migration from the medial portion of the arterial wall, proliferate and secrete extracellular matrix proteins that form a fibrous plaque. The migration of SMCs is influenced by low levels of NO, inflammatory response, physical factors like blood flow, matrix stiffness and sheer stress etc. Curcumin, the active constituent of *C. longa*, has been reported to prevent SMCs migration by inhibiting MMP-9 expression (Yu and Lin, 2010). Sulforaphane, an active constituent from *Brassica oleracea* var *italica*, has been found to inhibit smooth muscle cell proliferation and migration by reducing MMP-9 activity via the Ras and RhoA/ROCK pathways (Hung *et al*., 2013).

CONCLUSION

Pathophysiology of atherosclerosis is very intricate, which is known to involve several mechanisms such as oxidation of LDL, endothelial cell dysfunctioning, lipoprotein level modification, adhesion of molecules, SMCs migration, plaque formation etc. Therapeutic agents available for the treatment of atherosclerosis produce their effect through one or more mechanisms. In case of plants, several chemical constituents are present and these chemical constituents work through different mechanisms. Although herbal medicines and phytochemicals provide an excellent option to the menace of atherosclerosis, still their utilization in treatment of atherosclerosis is very limited. Present curiosity in traditional medicine has led to the exploration and development of many herbal drugs for the management of atherosclerosis. Moreover, comparing the risk and benefit ratio of synthetic agents with therapeutic agents from herbal sources, it was found that herbal sources have upper edge in benefit due to less side effects. Judicious use of herbal drugs (based on their mechanism of action) in management of atherosclerosis can provide an alternative platform.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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