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RESEARCH ARTICLE

NUTRACEUTICALS: A BETTER ALTERNATIVE TO STATINS IN THE FIGHT AGAINST ATHEROSCLEROSIS? - A REVIEW

Hari Priyaa G, Dr. Sinjitha S Nambiar and Dr. Sunil S. More
School of Basic and Applied Sciences, Dayananda Sagar University, Kumaraswamy Layout, Bangalore - 78, Karnataka, India.

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Abstract

Atherosclerosis: A major cause of death in today's world- is an inflammatory disease resulting from high plasma concentrations of cholesterol, especially that of Low - density lipoprotein (LDL). It leads to formation of lipid laden plaques which later blocks coronary arteries leading to heart attacks. Current medications used for the treatment and prevention are statins. However, statins have dangerous neuronal side effects. Traditional System of medicine in India- Ayurveda lists medicines which also serve as food in our daily lives, hence the name **Nutraceuticals:** The knowledge of these Nutraceuticals is currently being integrated into therapeutic regimen, considering the serious side effects of allopathic drugs. Medicinal plants have wide range of anti-atherosclerotic compounds many of which are as yet unexplored. Many of these plants have even shown reversal of atherosclerotic plaques. The present review provides a comparison of the action of Nutraceuticals with statins and shows how statins could one day be replaced with Nutraceuticals as the major therapy for atherosclerosis.

Introduction: -

Atherosclerosis is an inflammatory disease of the coronary arteries, leading to plaque formation which causes thinning of the arterial lumen ultimately leading to blockage of arteries and termination of blood supply to the heart resulting in heart attacks (1). Fatty streaks are formed by an interaction between lipoproteins circulating in the blood, cytokines, vascular smooth muscle cells, macrophages, in an environment of insulin resistance, hypertension and dyslipidemia (2). The plaque can also dislodge and move to other areas in arteries leading to stroke. Circulating oxidized LDLs are taken up by macrophages and these in turn get transformed to foam cells. The activation of macrophages by ox-LDL leads to the release of cytokines like interferon γ (IFN-γ), interleukin-1β (IL-1-β), interleukin -6 (IL-6), tumor necrosis factor α (TNF-α) which causes further Monocytes migration into the sub-endothelial space (3). In the subendothelial space, these monocytes differentiate into macrophages and start phagocytizing the lipids via scavenger receptors like lectin like oxidized LDL receptor (LOX-1), scavenger receptor A (SRA), CD36 and get converted to lipid-laden foam cells (1, 4-5). These foam cells thereupon become static and are unable to migrate which lead them to accumulate resulting in an inflammatory condition which sets the ground for plaque development. Sustained inflammation results in increased proliferation of macrophages and more inflammation leading to necrosis of foam cells. These dead cells accumulate and stimulate vascular smooth muscle cells to migrate from tunica media to tunica intima via inflammation. These cells form a layer and enclose the dead foam (lipid- laden macrophage) cells and form a capsule (plaque) within the arterial lumen reducing the diameter of

Corresponding Author: - Dr. Sinjitha S Nambiar.
Address:- School of Basic and Applied Sciences, Dayananda Sagar University, Kumaraswamy Layout, Bangalore - 78, Karnataka, India.

the lumen, thus decreasing the volume of blood flow to the heart. The fatty streak lesion later progresses to form complex lesions that cause stenosis to limit the blood flow to the heart. These complex lesions ultimately form the sites where thrombosis occurs leading to myocardial infarction (6).

Mechanism Of Atherosclerosis: -

The first cellular components in lesion formation are known as macrophages. ox-LDL through scavenger receptors taken up by macrophages, like scavenger receptors-A and CD36 that are not subjected to down regulation via a feed-back mechanism like LDL receptor. Inflammatory response by the macrophages is caused by the uptake of ox-LDL by these scavenger receptors results in the secretion of cytokines. Macrophages continue the process of Ox-LDL uptake and accumulation of lipids from Ox-LDL resulting in the formation of lipid filled foam cell which constitute the premature cellular phase of lesions. Foam cells can also remove lipids from the sub-endothelial area through ATP-binding cassette transporters such as ABCA1, ABCG1 which in additional carried by high-density lipoprotein (HDL) to advance metabolism. The process of cholesterol deduction is decreased causing the macrophages to accumulate lipids continuously as the plaque advances, causing in the death of these cells followed by the release of intracellular molecules which leads to assiduous chronic inflammation (7).

The inflammation causes smooth muscle cells to migrate from the tunica media to tunica intima, multiply and rearranges in the extracellular matrix (8). This results in the formation of the fibrous atherosclerotic plaques. The resultant lesion is characterized by calcification (sclerosis), which makes artery wall firm and fraileventually leading to the rupture of the covering endothelium causing the formation of thrombus and intravascular coagulation.

Effect Of Ox-Ldl On The Signal Transduction Pathway: -

Ox-LDL activates epidermal growth factor receptor (EGFR) which then causes the phosphorylation and activation of Akt. Activated Akt phosphorylates and activates P38 MAP kinase (9) and also activates nuclear factor erythroid 2 related factor 2 (Nrf2) (10). Nrf2 activation leads to augmented expression of CD36 leading to increased ox-LDL uptake in macrophages and foam cell formation. Akt activation, in addition to activating P38 MAP kinase, also activates nuclear factor (NF)-κB pathway which in turn leads to cytokine secretion thus enhancing inflammatory process. *Emblica officinalis* extracts have been shown to inhibit NF-κB activation in osteoclast cells (11). P38 activation in macrophages by ox-LDL also leads to multiplying (12). Migration Inhibition and apoptosis in future stages which ultimately plays a role in plaque formation (13). Henceforth this pathway is important for plaque development. Atherosclerotic plaque formation progresses with the proliferation, inhibition of migration, foam cell formation, followed by apoptosis of macrophages and resultant inflammation, inhibition of all these steps could highly decrease the development of the ailment.

Nutraceuticals And Molecular Pathway: -

Various plants and their Nutraceuticals have been found to reduce the formation of plaque by different mechanisms. Recent research has revealed many oral hypolipidaemic compounds from plant of ayurvedic reputation and many of these compounds showed potent anti-atherosclerotic activity. Allium sativum is one such plant rich in hypolipidemic compounds. It is extremely beneficial in counteracting many cardiovascular diseases by many mechanisms including reversal of atherosclerotic plaques (14). Allium sativum extracts have many chemical compounds. One such compound being allicin counters atherosclerosis by causing about cholesterol efflux in foam cells by upregulating efflux receptor like ABCA1, blocking many pathways involved in atherosclerosis like downregulating scavenging receptor like CD36, inhibiting NFκB etc. Reverse plaque in hypercholesterolemic rabbit models has been reported in E. officinalis fruit extract (15).

The extract of Agaricus blazei has been shown to prevent the activation of Akt and P38 by ox-LDL in macrophages. It prevents the development and buildup of foam cells and increase macrophages. Kaempferl is the compound has been shown to down regulate Akt activation in human glioma cells and has been found to be present in E. officinalis also. And it is also shown to reduce serum cholesterol levels in rats and reduction in NF-κB activation and cycloxygenase (COX-2) expression (16). Hypercholesterolaemic rabbits fed with E. officinalis fruit extract for 4 months has been shown to bring about a reversal of dyslipidemia, intimal and medial thickening and plaque formation in the aorta of rabbits and also controls the lumen of the aorta to the level of the normal control group, the ability to prevent low-density lipoprotein oxidation and to lower cholesterol synthesis by inhibition of 3-hydroxy-3-methylglutaryl-Coenzyme A reductase activity (15). It could also elevate high- density lipoprotein level and thus enhance reverse cholesterol transport.

When there is no enough oxygen to the myocardium it causes angina in case of cardiovascular diseases (CVD's). different medicinal plants extracts are prescribed for the treatment of CVDs for example; Tinosporacardifolia (17), Allium sativum, Emblica officinalis, Withania sominfera, Crocus sativa, Saussurea costus and Salvia officinalis were traditionally used plants for healing heart diseases (18). Scutellaria strigillosa ethanol extract has a flavonoid which acts as the anti-proliferative and anti-migratory activities against vascular smooth mucle cells. The mechanism involved is the upregulation of SM22α expression, henceforward inhibits ROS generation, and phosphorylation of ERK (19).

On the other hand, Atorvastatin and Fluvastatin, inhibit CD36, but also inhibit ABCA1 and hence inhibit cholesterol efflux (an undesirable side effect) (20,21). Thus, in contrast to the multitargeted approach of plant compounds, each of the statins target only one pathway and are wrought with treacherous side effects like memory loss, neuropathy, type 2 diabetes etc.

The below table 1 represents about the Nutraceuticals compounds acquiring efficient cardio-protective activity and table 2 describes about current therapies for atherosclerosis and their Shortcomings.

Table 1:- Nutraceuticals Compounds Acquiring Efficient Cardio-Protective Activity.

Compound	Mechanism of action	Reference
Rutin in Buckwheat	1. Inhibits ERK and AKT activation, 2. Inhibits NF-κB activation in inflammatory mice model 3. CD36 downregulation, Upregulates ABCA1 in obese mice model, inhibits proliferation and migration of VSMC	(22-24)
Allicin and s-allylcysteine in Garlic	1. Suppress P38, 2. CD36 downregulation, 3. Inhibits NFκB activation, 4. Upregulation of ABCA1 in macrophage derived foam cells 5. Inhibits proliferation and migration of VSMC	(25-27)
Garcinol in Garcinia indica	1. Downregulates NF-κB, Downregulates p42 MAP Kinase in rat models 2. Down regulates ERK in cancer cell lines 3. Increased ABCA1 and ABCG1 in mice model 4. Inhibits proliferation and migration of VSMC	(28-30)

Table 2:- Current Therapies for Atherosclerosis and Their Shortcomings.

Therapy	Common Drug	Mechanism	Side Effects
Statins (lowers bad cholestrol) (Li., Chen and Mehta., 2001)	Atorvastatin (Lipitor)	1. Inhibits ERK, 2. Fails to regulate ABCA1(31)	Muscle pain, digestive problems and mental fuzziness in some people and causes liver damage
	Fluvastatin (Lescol)	1. Promotes migration of VSMC 2. Suppresses ABCA1 (Undesirable effect) (32-33)	
	Simvastatin (Zocor)	1. Upregulation of CD36 in presence of ox-LDL 2. Promotes migration of VSMC in presence of ox-LDL (17, 34)	
Nicotinic acid	Niacin (Improve Overall Cholesterol)	1. Fails to activate ABCA1 2. Promotes migration of VSMC (35)	1. Increase Blood sugar levels, uncomfortable Skin flu shing

Conclusion: -

Atherosclerotic plaque not only causes myocardial infarction but also dislodges from coronary arteries, gets into different blood vessels and blocks these arteries causing stroke. Statins are beneficial in keeping the disease under control but do not reverse the plaque once formed. Plant extracts and their compounds have advantages over statins

in that they target multiple pathways at the same time and are devoid of side effects. However, each type of statins (even though they prevent cholesterol formation) tend to upregulate scavenging receptors or downregulates efflux receptors which aggravates the disease and are wrought with plenty of dangerous side effects. Thus, considering the imperfect treatment approach of statins, plant compounds with their multi-dimensional treatment modes, without any side effects, may become the drug of choice for the common masses in the near future hence forth it can enter the phase of clinical trials.

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