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Review Article

ROLE OF HERBAL NUTRACEUTICALS IN PREVENTION AND TREATMENT OF ATHEROSCLEROSIS

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ABSTRACT: Atherosclerosis falls under non communicable chronic diseases (NCDs), which is of great concern as identified by WHO, as one of the major causes of pre-mature mortality. Early studies have identified several molecular targets related to epigenetic factors and changed life style, psychosomatic issues and food habits as the cause of its pathogenesis. Since it is a progressive inflammatory disorder so its early detection and proper intervention could prove to be an effective tool in preventive-cardiology. Only management of diabetes, obesity, dyslipidaemia and hypertension may not be enough. Rather targeting factors responsible for induction of low-grade inflammation would be better option. Immune checkpoint proteins play a pivotal role in atherosclerosis by regulating the activation and proliferation of various immune and non-immune cells, such as T-cells, macrophages and platelets. The immune checkpoint stimulators specifically promote cell survival of T-cells, macrophages and platelets in atherosclerotic lesions and in secondary lymphoid organs, resulting secretion of more proatherogenic cytokines and chemokines. The role of platelets in activation of undesired innate immunity has also been extensively studied. Its main interaction with endothelial cells and immune cells is under focus of studies. The normalization of innate immunity and Toll-like receiptors (TLR) signalling by using nutraceuticals could be a promising approach in this field. These include medicinal plants, fruits, vegetables, legumes etc. Presence of several secondary metabolites as natural cocktail have synergistic response in these regulatory pathways, with lesser adverse effects. However, their safety margins, drug-drug interaction with allopathic medicines etc. must be ascertained. The role of some medicinal plants of Indian medicine (Ayurveda), which have experimental evidences for their therapeutic claims as anti-inflammatory and antioxidants are discussed here.

Key words: Atherosclerosis, Nutraceuticals, Herbal, Food Supplements, Ayurveda.

INTRODUCTION

Due to the rising disease-burden of obesity, diabetes and hypertension, the number of patients of cardio vascular diseases (CVD) are also increasing (Apovian *et al*. 2015, Dandona *et al*. 2017). The formation of plaque in the coronary-artery restricts the blood supply to heart muscle, resulting gradual weakness, and finally apoptosis of cardiac muscle fibres. It is primarily attributed to insufficient blood flow to target organs, due to blockage in arteries, which are supplying blood to these organs. When it is in vessels of heart (coronary artery) it is called atherosclerosis, when it is in brain, then it is called thrombosis and when it is major blood vessels supplying to lower extremities then it is peripheral vascular artery disease (Ross 1999).

RISK FACTORS AND SYMPTOMS

The early symptoms of atherosclerosis involve ischemia, arrythmia, cardio-respiratory discomfort, gastric angina and other symptoms (Oxenkrug 2010). However, after the burst of the vulnerable plaques, there is heart attack leading to morbidity and mortality. The death due to heart attack is one of the major contributors of total pre-mature deaths in the world. Earlier coronary bypass was the main line of treatment but now angioplasty, ballooning etc. are the main line of treatment.

Earlier, it was thought that hyper-lipidemia is the primary cause of genesis of atherosclerosis but in early 90s, it was postulated that inflammation is the primary cause,

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which may be linked to variety of causes like oxidative stress, infection, hypoxia, pH variation etc. (Libby *et al*. 2002, Hotamisligil 2006, Castro *et al*. 2017). Accumulation of advanced glycation end products (AGEs) or advanced oxidation protein products (AOPPs) has been identified as a risk factor for accelerated atherosclerosis (Ross 1999) (Fig. 1).

BASIC MECHANISMS

The basic causes behind all these diseases are the abnormal functioning of the blood vessels, which consists of 3 layers. The outermost layer is tunica externa followed by the media and intima, which is covered with an additional layer of the endothelial cells (ECs). It plays a significant role in regulating the dilation/relaxation property of the blood vessel. It is in direct contact with blood and its content, consisting of food digests, hormones, enzymes, neurohumors and all other contents found in the body fluid. In other words, the essence of metabolic and physiological changes is found in the blood, which overall affect the physiology of endothelial cells. This is governed by genetic and epigenetic factors, which affect both psychic (brain and its thoughts) and somatic (body) organs (Oxenkrug 2010, McKay and Mathers 2011).

Role of hyper-lipidemia in pathogenesis of atherosclerosis

In the blood, there are different types of lipoproteins to carry the lipid molecules in the blood, called HDL, LDL, VLDL and chylomicrons. When they are in excess, they enter in the tunica intima layer, by passive diffusion through the endothelial layer (ectopic fat deposition). During this process the endothelial dysfunction (ED) takes place. These endothelial cells undergo inflammation and secrete free radicals (FR) and inflammatory cytokines. The free radicals attack the unsaturated bonds of lipids in LDL (circulating low density lipoprotein) and produces oxidized LDL (oxLDL), which are not native to the body and needs to be removed. The FRs also attack on glucose molecules in different glycoproteins and produce AGEs (advance glycosylated entities). They are also not native to body and behave as foreign particles. These factors activate innate immunity, specifically the scavenger cell macrophages for removal of these modified macromolecules (Libby *et al*. 2002, Hotamisligil 2006, Castro *et al*. 2017).

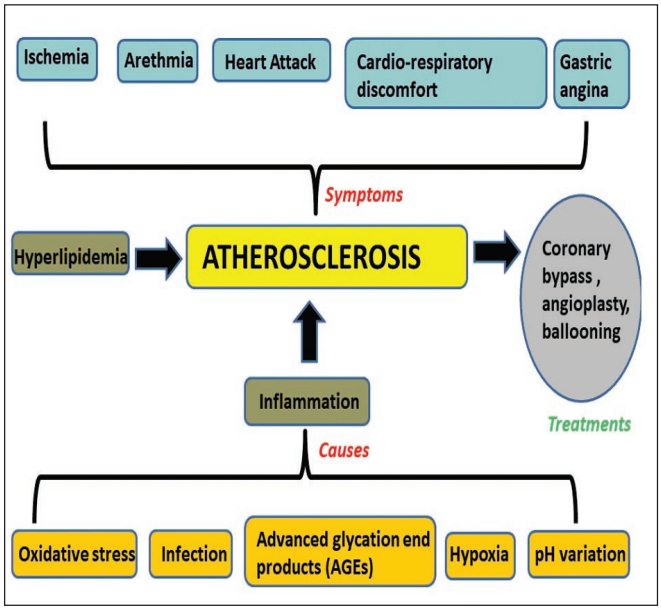

Fig. 1. Schematic diagram showing the causes, symptoms and treatments of Atherosclerosis

Cellular changes during activation of innate immunity

The macrophages are produced after differentiation of monocytes under the influence of MCSF (macrophage colony stimulating factor). They also activate the high rate of expression of scavenger receptors on their cell membrane, named as LDL-receptor-1. They also induce the EC to secrete monocyte chemoattractant proteins-1 (MCP-1), which attracts more monocytes to the tunica intima layer. The LDLr-1, described above, are specific to oxLDL and allow their uptake into the macrophages. Since the uptake of oxLDL is not under feedback control, allowing its excess accumulation within the cells and get converted to foam cells. The whole process takes place in tunica intima. These cells also exposed to less oxygen and higher metabolic rate, resulting a state of hypoxia, leading further cellular stress and finally induction of apoptosis of foam cells. The accumulation of dead macrophages activates fibrosis, become harder and called plaque. It is lipid loaded necrotic core (Oxenkrug 2010, Boutens and Stienstra 2016).

Pathogenesis of Heart attack

The cell debris (Plaque) are embedded in the arterial wall and covered with smooth muscle cells, which are kept on dying and forming a fibrous cap called ECM (extra cellular matrix). In fact, this is an adaptive process to protect the plaque from undergoing disruption. However, since the dead foam cells in plaque activate proteolytic enzyme called MMP (matrix metallo proteinases), there is always a chance of plaque disruption, a cause of heart attack.

When there is an imbalance of ECM synthesis and degradation, then vulnerability of plaque rupture is enhanced. This results to the release of stored lipid of plaque in the blood vessel, stopping blood flow in that vessel and connected tissue. This is accompanied by

activation of circulating platelets resulting blood clot formation (Bennett *et al*. 2016, Anlamlert *et al*. 2017).

Interventional approaches to prevent atherosclerosis

This needs a multi targeted action, because of involvement of several molecules in overall metabolism. In management of atherosclerosis there could be two approaches. One is to target the causative factor and other is to target the genes/mRNAs involved in inflammation, hypoxia and apoptosis (Libby *et al*. 2002, Hotamisligil 2006, Castro *et al*. 2017).

As mentioned above, there is involvement of (1) hyperlipidemia, (2) low grade inflammation, (3) hypoxia, (4) oxidative stress, (5) apoptosis, (6) over activity of innate immune system, (7) excess secretion of inflammatory cytokines, (8) plaque formation, (9) activity of MMP resulting vulnerable plaque disruption and so on. Taking to holistic approach, it appears that oxidative stress is the primary cause resulting all other steps as branches of complication ultimately resulting one complete picture of atherosclerosis. Thus, treating the root cause and also managing the related metabolic pathways would be the best approach to target this disease pathogenesis.

Epigenetic interventions

Epigenetic reprogramming also plays important role in regulating innate immunity and modification of cytokine profiles. The epigenetic drugs, like inhibitors of DNA methyltransferase and histone deacetylase may also be tried. Reports have shown the role of several secondary metabolites on this process. These includes butyrate, curcumin, (-)-epigallocatechin-3-gallate, resveratrol, romidepsin, and trichostatin A. Thus, inhibitors of enzymes, responsible for acetylation and methylation *e.g*. DNA methyltransferase and histone deacetylase can be tried. The secondary metabolites of medicinal plants have shown promising inhibitory potential for these enzymes (Aquila *et al*. 2019, Nicorescu *et al*. 2019).

Immunological modulation in pathogenesis of atherosclerosis

Recent findings have emphasized to inhibit the trigger of innate immunity system by regulating the enzymes involved in epigenetic regulation of gene expression of all these molecules. The macromolecular crowding is another factor, affecting the cellular environment by changing the colloidal state of cytoplasm, resulting conformational changes in proteins. This affects the unwinding of genes and finally their expression.

The primary factor is endothelial dysfunction, which is preceded by endothelial cell damage. It follows the steps for formation of foam cells, accumulation of antigen presenting cells (APC), activation and recruitment of T cells. Collectively, all these changes stimulate the innate immune system.These complex macrophages (foam cells) finally become the source of secretion of inflammatory cytokines, establishing low grade inflammation (LGI). The high levels of IFNγ further stimulate the recruitment of macrophages, DCs and T-cells to the plaque, increase lipid uptake by macrophages and activate APCs (Gupta *et al.* 1997, Foks and Kuiper 2017).

Immunotherapy is another approach to reduce the over-activity of macrophages and T cells which are responsible for excess release of inflammatory cytokines and cellular infiltration to smooth muscle cell layer of blood vessels. Various immune checkpoint modulators, transforming growth factors, beta receptor inhibitors, and indoleamine-2,3-dioxygenase inhibitors are available which may be checked to retard this pathogenesis.

Similarly, the programmed cell death protein 1 (PD-1)/ programmed cell death protein ligand 1 (PD-L1) axis leading to the exhaustion of T-cell immunity in chronic infections may also be explored as chronic infection is also a cause of systemic low grade inflammation and oxidative stress in the body, which has been identified as the primary cause of endothelial dysfunction.

Physical activity is reported to be an important therapy for atherosclerosis and peripheral artery disease. It becomes more effective if accompanied with intermittent claudication (Livero 2019).

Human studies have shown inverse correlation between atherosclerotic burden and Heat Shock Protein 27 expression. It acts through inhibition of inflammation and lowering of serum cholesterol. This can be assessed by measuring the level of hs CRP (High-sensitivity C-reactive protein) and Acute phase serum amyloid A (SAA) in blood as their elevated levels are good predictors of cardiovascular risk in humans (Chiu *et al.* 2019). Similarly, high activity of Proprotein convertase subtilisin/kexin type 9 (PCSK9) is also risk for atherosclerosis (inverse correlation).

The psychological wellbeing is also important in regulation of cardiovascular disorders. Thus, modulators of Brain–gut interactions could be tried as they directly affect the symptoms of anxiety or depression, which play significant role in pathogenesis of atherosclerosis and other CVDs. A positive correlation has been reported between emotional symptoms (ESs) and carotid intima-media thickness. Similarly, sleep disorders and onset of atherosclerosis has also been reported.

The role of depression and anxiety in atherosclerosis is also evident by positive correlation between Serum N-

acetyl-β-hexosaminidase (HEX) with atherosclerosis specially in patients of diabetes (Chojnowska *et al*. 2018, Belem da Silva *et al*. 2019, Del Brutto *et al*. 2019).

The genesis of plaque formation begins at the young stage but significant symptoms appear only at late stage of life, may be after 35-40 years of age. Thus, it is advised to take precautionary steps in at younger age itself to prevent the onset of atherosclerosis with clinical symptoms. This can be easily achieved by active lifestyle to maintain the balance of calorie intake and expenditure by regulating food intake and physical activity. Besides, energy balance, avoidance of those food items which cause inflammation, acidic pH, more free radical generation may be avoided. These include fried foods, very high protein diet, high ratio of fat in the diet. The 3rd option is to use the food supplements as nutraceuticals, which consists of micro-nutrients and phyto-molecules (Ross 1999, Hotamisligil 2006, Castro *et al*. 2017).

The key micronutrients include a balanced diet of protein, lipid and carbohydrate, essential amino acids and fatty acids, PUFA, minerals and vitamins. Though the nutrition-management may play important role in disease management, but it cannot be a common recommendation for all people. It may change with race, ethnic variation, metabolic capacity, age, sex and environment. The epigenetic factors also play important role, which is mainly governed by external and internal environment of an individual. The mental thoughts, behaviour and synchronization with solar rhythm *i.e* circadian cycle are the factors which directly affect this part.

While recommending the nutraceuticals, besides the use of minerals and vitamins, the variety of plant products are also considered. It may include fruits and vegetables of different colours and seasons like spinach, carrots, peaches, and berries; the main staple foods like oats, whole wheat bread, and brown rice and also their processing as refined or crude. The fibre and nutrient content are collectively considered. In addition to regular food items, the products made up of spices and medicinal plants are also recommended as food supplements (Mahady, www.eolss.net). In case of non-vegetarian foods, the animals of all ecosystems may be recommended, because they have different ratio of active nutraceuticals in them. For example, fish from fresh water or sea water have different oily composition. The fish-meat from tuna, salmon, mackerel, lake trout, herring, and sardines are rich in omega-3 fatty acids (Kalra 2003, Oxenkrug 2010, McKay and Mathers 2011).

HERBS IN MANAGEMENT OF ATHEROSCLEROSIS

It has been given a new term as Nutrigenomics/ nutraceutical therapy and being considered as important tool in management of age related chronic metabolic diseases. It can be used at all the 3 levels of prevention *i.e.* primary prevention which may decrease the number of new patients, then secondary prevention, which lowers the rate of established cases of disease in the population (prevalence) and finally the tertiary prevention, which focuses on decrease the amount of disability associated with an existing disease. This whole process involves awareness and education about preventive measures, by early diagnosis, through population screening and management, by disability limitation and rehabilitation respectively. The doses and combination of plants would vary at different stages, because it may be used as supplement and also as medicine depending on the type of formulations (Roberts 1954, Kalra 2003, Solas *et al*. 2016).

SECONDARY METABOLITES

The pharmacological action of any plant is attributed to its phytochemicals, which are more than 100 in number. They are the secondary metabolites, synthesized by the plant to protect themselves from various atrocities and adverse environmental stresses. However, we use those Phyto molecules of our health benefits. They are found in medicinal plants, vegetables, fruits and seeds (Mahady, www.eolss.net). The legumes and dry fruits are prominently used. Depending on structural characteristics, they are broadly classified in different groups like polyphenols, flavones, flavonoids, phytosterols, phytoestrogens, terpenes, tannins, alkaloids, etc. Mostly they possess the aromatic ring or double bonds capable to delocalize the electrons of the free radicals, making them inactive. This process is called free radical (FRs) scavenging property, thus used as antioxidants to reduce the oxidative stress, which is induced in the body by high metabolic state of a cell (beyond the normal capacity). However, besides this potential, many of them have direct action on the signalling pathways of synthesis of enzymes, hormones and other proteins, which are responsible to regulate the overall physiology of a cell. Some of them block the receptors, other work through epigenetic mode and binds to the promoters. Some regulate the activity of kinases and phosphatases, playing an important role in signal transduction, post receptor activation by a hormone/ other biomolecule in a cell. Here we describe some of the plants which are rich in those phytochemicals, which

have shown evidence to prevent the progress of pathogenesis of plaque formation or its instability processes (Libby *et al*. 2002, McKay and Mathers 2011, Castro *et al*. 2017).

Flavonoids

Flavonoids comprise the most common group of plant polyphenols and provide much of the flavour and colour to fruits and vegetables. More than 5000 different flavonoids have been described and they broadly grouped into 6 forms such as flavones (*e.g.* apigenin, luteolin and apigenin), flavanols (*e.g*. quercetin, myricetin, kaempferol), flavanones (*e.g.* naringenin, hesperidin), catechins or flavanols (*e.g.* epicatechin, Gallo catechin), anthocyanidins (*e.g*. cyanidin, pelargonidin), and isoflavones (*e.g.* genistein, daidzein). They are mostly found as glycosides and attributed with strong anti-oxidant potential. Quercetin, the major representative of the flavanol subclass, is a strong antioxidant potential. Flavonoids present in foods were considered non-absorbable because they are bound to sugars as beta-glycosides. Only free flavonoids without a sugar molecule, the so-called aglycones, were thought to be able to pass through the gut wall. Hydrolysis only occurs in the colon by microorganisms, which at the same time degrade flavonoids. Contrary to this the quercetin glycosides from onions were absorbed far better than the pure aglycone (Hollman and Katan 1998, Bell *et al*. 2015).

Phytosterols

Phytosterols are another group of phyto-molecules, which is structurally similar to cholesterol but synthesized in plants. It interferes with the absorption of dietary cholesterol in the intestine (Lin *et al.* 2009). Thus, it lowers the state of hyper cholesterolemia. Similarly, anthraquinones, an aromatic compound with 3 rings and the keto groups are located on the central ring. It is the main constituent of colored pigments in plants. They have shown anti-obesity property and sesquiterpene lactones have shown anti-inflammatory role by down regulating the gene for enzymes like COX2, iNOS, or ILl β (Mahady, www.eolss.net, Apovian *et al.* 2015).

Phytoestrogens

Phytoestrogens (PE) are another group of secondary metabolites and are naturally found as their glycosides, which are hydrolysed in the intestine. In the intestine, the microbiome metabolizes these phytochemicals to another molecule for proper absorption. As the name indicates, PE are similar to oestrogens and very effective in post-menopausal syndrome related disorders including atherosclerosis and systemic low-grade inflammation (Libby *et al*. 2002, Hotamisligil 2006, Castro *et al*. 2017).

These are classified as flavonoids, isoflavonoids, coumestans, stilbenes, lignans and terpenoids. Isoflavones are a subclass of flavonoids, where one phenolic ring has migrated from C-3 to C-2 (King and Young 1999). The Soybean is richin isoflavones like genistein, daidzein and their methyl ether derivatives, biochanin A and formononetin. The Terpenoids (ferutinine, tschimgine, and tschimganidine) found in the Umbelliferae family have estrogenic activities. They are very rich in plants of the family Leguminosae. Further 2,3,4',5-tetrahydroxystilbene 2-O-beta-D-glucoside has been shown to improve the vascular endothelial dysfunction and prevented changes of eNOS and iNOS expression, leading to preservation of Nitric Oxide (NO) bioactivity. A poly-phenol, namely salvianolic acid B from *Salvia miltiorrhiza* suppresses the expression of ICAM and VCAM (Hung *et al*. 2010). Thymoquinone (TQ) from *Nigella sativa*, Dachaihutang and Paeonol from other plant sources have shown antioxidant and anti-atherosclerotic potential. The phytomolecules like danshensu (DSS), tanshinones (cryptotanshinone, CT) and Ferulic acid (FA) have shown anti-atherosclerotic and anti-vascular restenosis potentials along with protection of vascular smooth muscle cells (VSMC) by injury induced by free radicals. Icariin (2-(4' methoxylphenyl)-3-rhamnosido-5-hydroxyl-7-glucosido-8-(3'-methyl-2-butylenyl)-4 chromanone) is a flavonoid isolated from *Herba epimedii*, is widely used for the treatment of atherosclerosis and neuropathy.

SOME MEDICINAL PLANTS OF THERAPEUTIC IMPORTANCE

Herbals like black cohosh, chamomile, chasteberry, lavender, passionflower, and saffron appear useful in mitigating anxiety or depression. In Ayurveda, about nine medicinal plants have been clubbed as "Madhya Rasayana" (nootropic drug). These needs to be tried in patients of atherosclerosis. Not much studies have been carried out in this respect. *Bacopa monnieri* (L) Wettst (common name, bacopa) has been reported to inhibit inflammatory pathway in Brain through inhibition of release of inflammatory cytokines TNF-α and IL-6 (Maslov and Karpov 2017, Nemetchek *et al*. 2017, Yeung *et al.* 2018).

Although pure phytochemicals are used for developing synthetic drugs for use in modern system of medicine, the crude medicinal plants have their own importance. They are the natural cocktail of several secondary

metabolites, minerals, vitamins, fibres and oils. They are used as food supplements and also as home-made medicines to tackle the day to day health problems. Many foods like berries, nuts, extra virgin olive oil, rich in phenolics, have shown physiological effects, thus pave a path for further research (King and Young 1999). Bioactive polyphenols include flavanols (*e.g*, onions, broccoli, tea, various fruits), flavones (in parsley, celery, chamomile tea), flavanones (in citrus fruits), flavanols (flavan-3-ols) such as catechins and procyanidins (in cocoa, apples, grapes, red wine, tea), anthocyanidins (in colour berries), and isoflavones (in soy). Flavonoid-rich cocoa, dark chocolate has shown preventive response on CVD in some of the clinical studies, through raised eNOS (endothelial nitric oxide production). In this series, some plants are being described below, which have shown the therapeutic importance towards the management of obesity, hyper-lipidemia and atherosclerosis progress. The composition of many plant extracts collectively shows multi-targeted action by simultaneously inhibiting cholesterol absorption, decreasing blood LDL levels, increasing blood HDL levels, act as PPAR α agonists, modify inflammatory markers and hypo-cholesterolemic agent and lower Blood Pressure (BP). The plant combinations of L-theanine and EGCG, Goldenseal plant; rhubarb, turmeric, Astragalus root, red sage root, and ginger root are in clinical use. Garlic (*Allium sativum* L.) is rich in alliin which is converted to allicin, by an enzyme alliinase, which is released after its crushing. It is an organo-sulphur compound and has shown hypolipidemic, anti-inflammatory and antihypertensive potentials (Aviello *et al*. 2009, Vazquez-Prieto *et al*. 2010, Liu *et al*. 2017).

The products derived from *Termenalia arjuna*, *Strychnox nuxvomica*, *Boswellia serrata*, *Commiphora mukul*, *Semecarpus anacardium*, *Inula racemosa* and *Bacopa monnieri* have shown significant anti-atherosclerotic response in different experimental models (Satyavati *et al*. 1969, Chaturvedi *et al*. 1995, Tripathi *et al*. 1998).

BHUx

Though several products are in the market, but a product named as BHUx, has been developed by our group at Banaras Hindu University (BHU), India. It has shown significant improvement in diet induced atherosclerosis. It has been patented in USA, China and European Union and also in India and it has been found to be effective to reduce Ox-LDL, to inhibit lipoxygenase-15 (LOX-15) and cyclooxygenase-2 (COX-2), to stabilize atherosclerotic plaque by strengthening the collagen cap

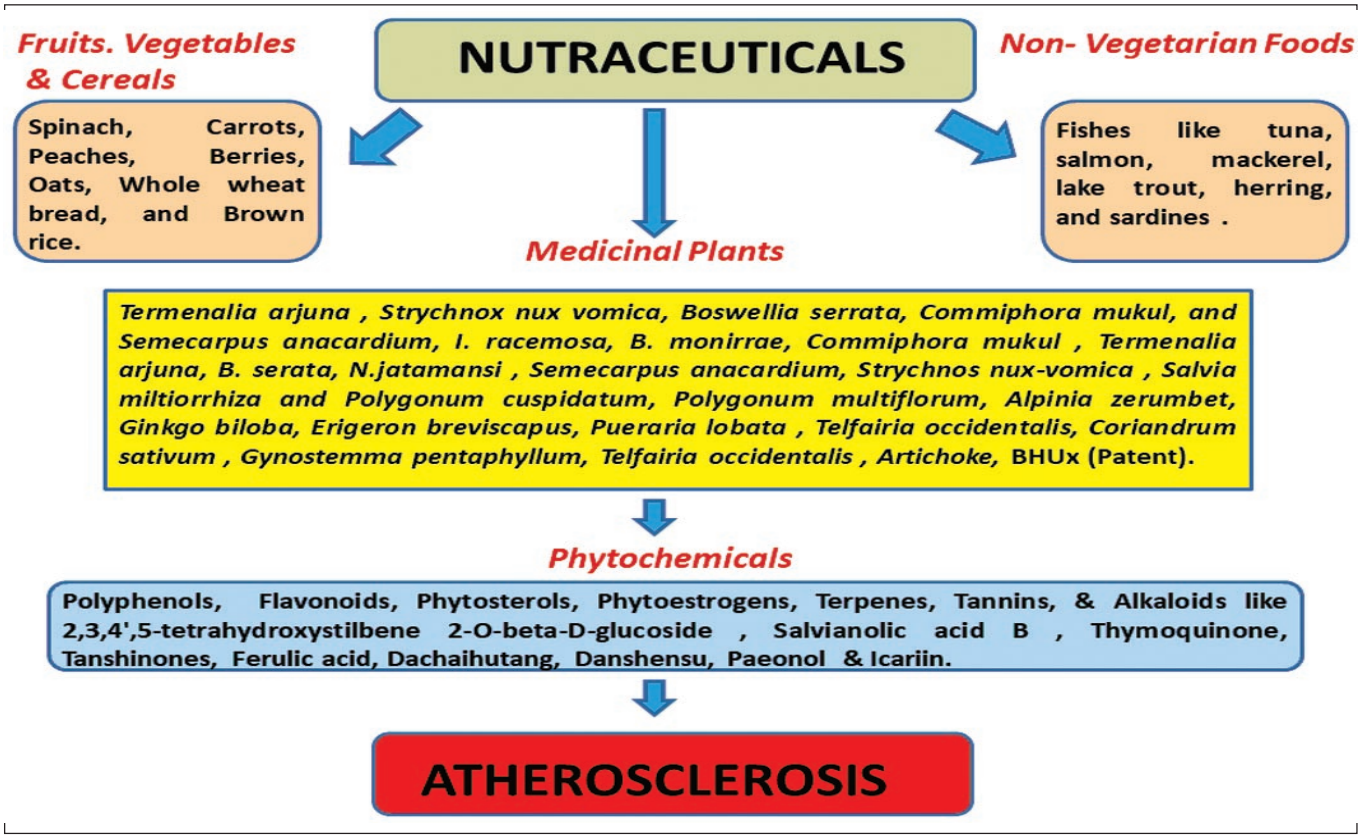

Fig. 2. Summary of potential nutraceuticals against Atherosclerosis.

and to reduce the calcification in plaque and to scavenge free radicals (Tripathi 2009).

Guggul

Guggul, the resin of tree of *Commiphora mukul* (Hook, ex stocks) Engl. (syn. *Balsam odendron* mukul Hook), is used as medicine after proper purification. Its active compound is Guggul-sterones, which has two isomers *i.e.* Z and E-stereoisomer. Recently, its action on two nuclear hormone receptors, involved in cholesterol metabolism, has also been reported. It is the most common medicinal plant of Ayurveda, used for obesity and inflammation. Its mechanism of action has been proved to be through activation of the thyroid gland, especially in cases of sub-clinical hypothyroidism (Agarwal *et al*. 1986, Tripathi *et al*. 1988, Liu *et al*. 2017).

Termenalia arjuna

The extract of bark of *Termenalia arjuna* is very effective in regulating tachycardia, blood pressure and arethmia. Its action has been reported to be through Ca^{++} channel blocking mechanism. It also inhibits the activity of adenosine deaminase, involved in pathogenesis of hypertension (Tripathi 1993).

Boswellia serrata

The resin of *Boswellia serrata*, rich in Boswellic acids, penta cyclic triterpenic acids, shows anti-inflammatory properties.

Inula racemosa

The rhizome of *I. racemosa,* rich in isoallantolactones is effective in treating angina pain. Its mechanism is proposed through β -blocking activity (Chaturvedi *et al*. 1995).

OTHER POTENTIAL HERBALS

The plants like *Bacopa monnieri* and *Nardostachys jatamansi* have been associated with significant antioxidant and neuro-modulating potentials. The plants like *Semecarpus anacardium* (Tripathi *et al*. 1996, Tripathi *et al*. 1998) and *Strychnos nux-vomica* have shown potential to reduce inflammation and nervous abnormalities respectively, which are the pathogenic factors behind atherosclerosis.

The plants of the Chinese system of medicine have also been well documented to manage atherosclerosis. They include *Salvia miltiorrhiza and Polygonum cuspidatum, Polygonum multiflorum, Alpinia zerumbet, Ginkgo biloba, Erigeron breviscapus*. The *Salvia miltiorrhiza* has shown hypolipidemic property through modulation of farnesoid X receptor. The *Alpinia zerumbet* (AZ), has shown to enhance high-density lipoprotein cholesterol (HDL-C). *Ginkgo biloba* extract (EGB) possess strong antioxidant and hypolipidemic potentials. *Erigeron breviscapus* has shown to enhance the acetylcholine-induced nitrate/nitrite production and increased the gene expression of endothelial nitric oxide synthase (eNOS), resulting vasodilation/vaso-relaxation. 2,3,4',5-Tetrahydroxystilbene 2- O-beta- D-glucoside (TSG), an active component extracted from Polygonum multiflorum, Paeonol, a major phenolic component of Moutan Cortex, thymoquinone (TQ), isolated form *Nigella sativa,* Dai-saiko-to (Da- Chai- Hu- Tang in Chinese) have shown anti-atherosclerotic potential (King and Young 1999, Yao *et al*. 2007, Hung *et al*. 2010).

Root extract of *Pueraria lobata* (Willd.) Ohwi (Fabaceae) has been shown to prevent oxidative stress and hyperglycemia. It is rich in puerarin, 3'-hydroxypuerarin, 3'-methoxypuerarin, 6''-xylosylpuerarin, daidzin, genistin, daidzein and genistein. Similarly, *Salvia miltiorrhiza* has been found to attenuate growth of smooth muscle cells (SMCs) under oxidative stress, such as homocysteine (Hcy) treatment. It has also scavenged the ROS in the system and subsequent modulation of protein carbonylation to inhibit cell proliferation. *Telfairia occidentalis* (fluted pumpkin) has been reported to have hypo-cholesterolemic role and its mechanism of action has been reported through the reduction of oxidative stress and cholesterol lowering effect. Both polysaccharides and vitamin antioxidants from *Lycium barbarum* fruits and also its crude extract have been associated with hypolipidemic effect. Extract of *Coriandrum sativum L*. also has similar property. Gypenoside (Gyp) XLIX, a dammarane-type glycoside, isolated from *Gynostemma pentaphyllum* (GP) is one of the prominent components in GP. Gyp XLIX to be a potent peroxisome proliferator-activated receptor (PPAR)-alpha activator. The rhizome of *Picrorhiza scrophulariiflora* (PS) has been shown to prevent the formation of AGEs (Adaramoye *et al*. 2007, Huang *et al*. 2007, Hung *et al*. 2010).

The dried leaves of artichoke contains up to 6% phenolic acids, including 3-O-caffeoquinic acid (chlorogenic acid), caffeic acid, 4-O-caffeoquinic acid, 5-O-caffeoquinic acid, 1,3-di-O-caffeoquinic acid, 1,5-di-O-caffeoquinic acid (cynarin); up to 5% sesquiterpene lactones, with cynaropicrin (King and Young 1999). *Telfairia occidentalis* (fluted pumpkin) is a useful therapy for high cholesterol and oxidative stress (Adaramoye *et al*. 2007) (Fig. 2).

CONCLUSION

Thus, it could be summarized that plant in totality and

also their isolated phyto-molecules have significant health benefits. Their preparations, doses, time of use and their combinations with other plants are important factors, when been used as food supplements for prevention and management of diseases. Besides life style change and use of allopathic, medicine along with medicinal plants may show dramatic changes in the field of health care. Although several pre-clinical data are available to evidence the therapeutic claims, but more focused clinical studies are the demand of time to spread its use by the common masses.

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REFERENCES

Adaramoye OA, Achem J, Akintayo OO, Fafunso MA (2007) Hypolipidemic effect of *Telfairia occidentalis* (Fluted pumpkin) in rats fed a cholesterol-rich diet. J Med Food 10: 330-336.

Agarwal RC, Singh SP, Saran RK, Das SK, Sinha N *et al*. (1986) Clinical trial of gugulipid—a new hypolipidemic agent of plant origin in primary hyperlipidemia. Indian J Med Res 84: 626-34.

Anlamlert W, Lenbury Y, Bell J (2017) Modeling fibrous cap formation in atherosclerotic plaque development: stability and oscillatory behavior. Adv Differ Equations 2017: 195.

Apovian CM, Aronne LJ, Bessesen DH, McDonnell, ME, Murad MH *et al*. (2015) Pharmacological management of obesity: an Endocrine society clinical practice guideline. J Clin Endocrinol Metab 100: 342-362.

Aquila G, Marracino L, Martino V, Calabria D, Campo G *et al*. (2019) The use of nutraceuticals to counteract Atherosclerosis: the role of the notch pathway. Oxid Med Cell Longev 2019: 1-30.

Aviello G, Abenavoli L, Borrelli F, Capasso R, Izzo AA *et al*. (2009) Garlic: empiricism or science? Nat Prod Commun 4: 1785-1796.

Bennett M R, Sinha S, Owens GK (2016) Vascular smooth muscle cells in Atherosclerosis. Circ Res 118: 692-702.

Belem da Silva CT, Hoffmann MS, Sant'Anna RT, Wehrmeister FC, Gonçalves H *et al*. (2019) Early emotional symptoms predicting carotid Atherosclerosis in youth: results from a birth cohort in Latin America. J Am Heart Assoc 8(2): e011011.

Bell L, Lamport DJ, Butler LT, Williams CM (2015) A review of the cognitive effects observed in humans following acute supplementation with flavonoids, and their associated mechanisms of action. Nutrients 7: 10290-19306.

Boutens L, Stienstra R (2016) Adipose tissue macrophages: going off track during obesity. Diabetologia 59: 879-894.

Castro AM, Macedo-de la Concha LE, Pantoja-Meléndez CA (2017) Low-grade inflammation and its relation to obesity and chronic degenerative diseases. Rev Médica del Hosp Gen México 80: 101-105.

Chaturvedi P, Shukla S, Tripathi P, Chaurasia S, Singh SK, Tripathi YB (1995) Comparative study of *Inula racemosa* and *Saussurea lappa* on the glucose level in Albino rats. Anc Sci Life 15: 62-70.

Chiu MH, Shi C, Rosin M, Batulan Z, O'Brien ER (2019) Biophysical analyses and functional implications of the interaction between Heat Shock Protein 27 and antibodies to HSP27. Biochim. Biophys. Acta 4165(19)30137-0.

Chojnowska S, Cabaj-Wiater I, Mikulska-Baran A, Zalewska-Szajda B, Waszkiewicz N (2018) Positive correlation of serum N-Acetyl- β -hexosaminidase with markers of Atherosclerosis in Diabetes type 2 patients with mild symptoms of depression and anxiety. Dis Markers 2018: 1-6.

Dandona L, Dandona R, Kumar GA, Shukla DK, Paul VK *et al* (2017) Nations within a nation: variations in epidemiological transition across the states of India, 1990-2016 in the Global burden of disease study. Lancet (London, England) 390: 2437-2460.

Del Brutto OH, Mera RM, Zambrano M, Simon LV, Matcha GV, Castillo PR (2019) Sleep quality correlates with the carotid intima-media thickness in stroke-free community-dwelling adults living in rural Ecuador. The Atahualpa project. Sleep Med 55: 22-25.

Foks AC, Kuiper J (2017) Immune checkpoint proteins: exploring their therapeutic potential to regulate atherosclerosis. Br J Pharmacol 174(22): 3940-3955.

Gupta S, Pablo AM, Jiang XC, Wang N, Tall AR, Schindler C (1997) IFN-γ, potentiates atherosclerosis in ApoE knock-out mice. J Clin Invest 99(11): 2752-2761.

Hollman PC, Katan MB (1998) Bioavailability and health effects of dietary flavonols in man. Arch Toxicol Suppl 20: 237-248.

Hotamisligil GS (2006) Inflammation and metabolic disorders. Nature 444: 860-867.

Huang T, Tran V, Roufogalis B, Li Y (2007) Gypenoside XLIX, a naturally occurring gynosaponin, PPAR-alpha dependently inhibits LPS-induced tissue factor expression and activity in human THP-1 monocytic cells. Toxicol Appl Pharmacol 218: 30-36.

Hung YC, Wang PW, Pan TL (2010) Functional proteomics reveal the effect of *Salvia miltiorrhiza* aqueous extract against vascular atherosclerotic lesions. Biochim Biophys Acta Proteins Proteomics 1804: 1310-1321.

Kalra EK (2003) Nutraceutical-definition and introduction. AAPS Pharm Sci 5: 27-28.

King A, Young G (1999) Characteristics and occurrence of phenolic phytochemicals. J Am Diet Assoc 99: 213-218.

Libby P, Ridker PM, Maseri A (2002) Inflammation and atherosclerosis. Circulation 105: 1135-1143.

Liu Y, Sun M, Yao H, Liu Y, Gao R (2017) Herbal medicine for the treatment of obesity: an overview of scientific evidence from 2007 to 2017. Evidence-Based Complement Altern Med 2017: 1-17.

Livero F, Junior Gasparotto A (2019) Non-genetic rats models for atherosclerosis research: from past to present. Front Biosci (Schol. Ed) 11: 203-213.

Mahady GB. Medicinal plants for the prevention and treatment of coronary heart disease. Ethnopharmacology 2. Encyclopaedia of life support systems. https://www.eolss.net/Sample-Chapters/C03/E6-79-16-00.pdf. Accessed on 20 April 2019.

Maslov LN, Karpov RS (2017) Prospects for the use of Cannabinoid receptor ligands for the treatment of metabolic syndrome and Atherosclerosis: analysis of experimental and clinical data. Ann Russ Acad Med Sci 72: 59-65.

McKay JA, Mathers JC (2011) Diet induced epigenetic changes and their implications for health. Acta Physiol 202: 103-118.

Nemetchek MD, Stierle AA, Stierle DB, Lurie DI (2017) The Ayurvedic plant *Bacopa monnieri* inhibits inflammatory pathways in the brain. J Ethnopharmacol 197: 92-100.

Nicorescu I, Dallinga GM, de Winther MPJ, Stroes ESG, Bahjat M (2019) Potential epigenetic therapeutics for atherosclerosis treatment. Atherosclerosis 281: 189-197.

Oxenkrug GF (2010) Metabolic syndrome, age-associated neuroendocrine disorders, and dysregulation of tryptophan-kynurenine metabolism. Ann N Y Acad Sci 1199: 1-14.

Roberts DW (1954) The Commission on Chronic Illness. Public Health Rep 69: 295-299.

Ross R (1999) Atherosclerosis an inflammatory disease. N Engl J Med 340: 115-126.

Satyavati GV, Dwarakanath C, Tripathi SN (1969) Experimental studies on the hypocholesterolemic effect of Commiphora mukul. Engl. (Guggul). Indian J Med Res 57: 1950-1962.

Solas M, Milagro FI, Martínez-Urbistondo D, Ramirez MJ, Martínez JA (2016) Precision obesity treatments including pharmacogenetic and nutrigenetic approaches. Trends Pharmacol Sci 37: 575-593.

Tripathi YB (1993) Terminalia arjuna extract modulates the contraction of rat aorta induced by KCl and norepinephrine. Phyther Res 7: 320-322.

Tripathi YB (2009) BHUx: a patented polyherbal formulation to prevent hyperlipidemia and atherosclerosis. Recent Pat Inflamm Allergy Drug Discov 3: 49-57.

Tripathi YB, Chaurasia S, Tripathi E, Upadhyay A, Dubey GP (1996) *Bacopa monniera* Linn. as an antioxidant: mechanism of action. Indian J Exp Biol 34: 523-526.

Tripathi YB, Tripathi P, Ramana Reddy MV, Dutt S, Tewari DS, Reddy EPK (1998) Effect of *Semicarpus anacardium* on the cell cycle of DU-145 cells. Phytomedicine 5: 383-388.

Tripathi Y, Tripathi P, Malhotra O, Tripathi S (1988) Thyroid stimulatory action of (Z)-Guggulsterone: mechanism of action. Planta Med 54: 271-277.

Vazquez-Prieto MA, Gonzaìlez RE, Renna NF, Galmarini CR, Miatello RM (2010) Aqueous garlic extracts prevent oxidative stress and vascular remodeling in an edxperimental model of metabolic syndrome. J Agric Food Chem 58: 6630-6635.

Yao P, Song F, Li K, Zhou S, Liu S *et al.* (2007) *Ginkgo biloba* extract prevents ethanol induced Dyslipidemia. Am J Chin Med 35: 643-652.

Yeung KS, Hernandez M, Mao JJ, Haviland I, Gubili J (2018) Herbal medicine for depression and anxiety: a systematic review with assessment of potential psycho-oncologic relevance. Phyther Res 32: 865-891.

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