ROS

REVIEW ARTICLES

Cardiovascular Diseases: Can Herb-Based Antioxidant and Anti-Inflammatory Functional Products Be a Solution?

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ABSTRACT | Cardiovascular health is vital for maintenance of life in man as well as animals. Inflammatory changes in the cardiovascular system are a common occurrence with today's lifestyle, but they generally go unnoticed unless they appear as a severe life-threatening clinical manifestation. The major cardiovascular risk revolves around three pathophysiological events, namely, oxidation of low-density lipoproteins, endothelial dysfunction, and release of inflammatory mediators. The effective management of cardiovascular diseases largely aims at reducing/delaying symptoms or affecting hemodynamic response and often does not affect the cause or course of disease, namely, the atherosclerotic lesion itself. Several Indian herbs carry tremendous restorative potential and can be successfully employed to achieve the therapeutic targets. Public awareness of the health benefits of herbs has motivated the common man to incorporate many of these in their dietary schedule, but many times their interactions result in serious clinical outcomes, which are generally misunderstood as side effects of medicines being prescribed by the physicians. Therefore, it becomes mandatory that the pharmacological role of the herbs used as spices and regular dietary ingredient or supplement be earmarked and judiciously used for promoting the health of the mankind. In this review, the much recommended use of herbal components as prophylactic functional foods is discussed with respect to the health benefits likely to be offered in cardiovascular issues and the threats imposed through them.

KEYWORDS | Atherosclerosis; Cardiovascular health; Herbs; Oxidative stress; Inflammation

ABBREVIATIONS | BP, blood pressure; COX, cyclooxygenase; CRP, C-reactive protein; CVD, cardiovascular disease; ICAM, intercellular adhesion molecule; LDL, low-density lipoprotein; oxLDL, oxidized low-density lipoprotein; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-alpha; VCAM, vascular cell adhesion molecule

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1. INTRODUCTION

The cardiovascular diseases (CVDs) have been reported as the major cause of morbidity and mortality over the last few decades in developed countries, and are emerging as new epidemics for developing nations like India [1]. The proactive busy lifestyle in the Indian cities has resulted in an increased dominance of high cholesterol, hypertension, osteoporosis, and diabetes in the human population. In 2003, the prevalence of cardiovascular diseases in urban Indians is reported to be 8–10% with an estimated loss of over 9.2 million years, which is likely to increase to 18 million years by 2030 [2]. The World Health Organization (WHO) has also predicted 2.5 million annual deaths by 2020 in the developed world [3]. The situation is alarming and needs the health professionals to look into suitable health promotion measures and steer the society for earlier CVD detection and management. Several factors have been found to predispose the individual to CVD in addition to their hereditary/genetic makeup, such as lifestyle, nutritional changes, industrialization, urbanization, and environmental pollution among many others.

In early days, it was presumed that exercising optimal control over blood pressure (BP) and blood cholesterol content can ensure the elimination/reduction of the cardiovascular risk, but soon the physicians were disillusioned. The death scores for cardiovascular problems certainly reduced after careful monitoring of BP and cholesterol in many countries, but a parallel increase in the incidence of obesity and type II diabetes was also observed. Moreover, the assumption did not prove to be valid for the traditional French diet which was high in saturated fats, but French people have a lower incidence of CVD as compared to Americans, a phenomenon known as the French paradox. To date, only a limited success has been recorded in controlling the prevalence and mortality from heart diseases. The plausible reason for this limited success might be a missing link between the blood pressure, lipid profile, and the CVD. Recent research has suggested that inflammation plays an important role in CVD. Therefore, the missing link might be inflammation taking place in the different tissues of cardiovascular system. The present review highlights the role of inflammation in the initiation and progress of CVD and the possible amelioration using herbs as a dietary constituent.

2. INFLAMMATION AND CARDIOVASCULAR DISEASES

Arterial inflammation/atherosclerosis is at the heart of any CVD [4]. Atherosclerosis develops in the arterial wall, portrayed by histological and physiological changes in large arteries, and remains asymptomatic until ischemia of distal organs becomes evident [5]. Atherosclerosis, free radical generation, and the resulting vascular disorders today present one of the major health issues in the modern medicine and public health domain. Although research depicts inflammation and oxidative stress as the major players for CVD, in actuality, these two participate in a wide variety of physiological processes. Inflammation is a principal attribute of the immune system that functions in the body to defend and preserve tissue integrity and function in situation of pathogenic assault or disease development; and in case of tissue injury, it recruits leukocytes and plasma proteins to the affected tissue site. However, chronic stimulation of immune system and consequently the unceasing inflammatory cascade lead to a continuous release of inflammatory mediators resulting in lasting vascular reactivity, hyperlipidemia, insulin resistance, and subsequently, give birth to a chronic disease.

Generation of free radicals is a normal physiological process that is required for the optimal functioning of the tissue metabolic processes [6]. The body maintains equilibrium between the oxidative stress and the antioxidant potential of the tissues. Whenever, the equilibrium is disturbed, either in case of pathological or altered physiological conditions, the body induces an adaptive response, known as para-

inflammation [7]. This response relies mainly on activation of tissue macrophages as a part of inflammatory cascade, and the intensity of the response ranges between the basal homeostatic state and a classic inflammatory reaction. Parainflammation is probably base root of the chronic inflammatory conditions which represent, today, the basis for the development of the multifactorial diseases, encompassing both chronic inflammatory rheumatic disorders and a wide variety of conditions including type 2 diabetes, cardiovascular and neurodegenerative diseases, obesity, cancer, asthma, and ageing [8].

3. MOLECULAR MECHANISMS OF NUTRITIONAL OXIDATIVE STRESS-INDUCED CARDIOVASCULAR PARAINFLAMMATION

Oxidative metabolism of dietary constituents is a foundation of human and animal life. The dietary nutrients provide energy for vital body processes through glycolysis, oxidative phosphorylation, and intermediary metabolism. All these processes include direct incorporation of oxygen atoms from molecular oxygen into biomolecules, and in so doing, result in the formation of reactive oxygen intermediates, more commonly known as reactive oxygen species (ROS), which can damage biological molecules [9, 10]. The term "nutritional oxidative stress" refers to an imbalance between the prooxidant load (i.e., excessive production of reactive oxidative metabolites) produced as a result of dietary metabolic processes and an inadequate dietary supply of antioxidants. Different components of diet vary in their oxidative potential as well as their antioxidant role in the body [11]. Plant-based foods (e.g., fruits and vegetables, wine, nuts, natural vegetable oils, and whole grains) have been an important component of traditional diets in Mediterranean regions. A large and consistent body of scientific evidence demonstrates that diets rich in plant foods provide protection against CVD, several common types of cancer, and other chronic human diseases [12].

In contrary, diet rich in lipids and/or carbohydrates increases the susceptibility of the living being toward oxidative damage [13, 14]. These biomolecules are readily present in a prooxidant state in the diet or serve as targets of oxidative modifications after their intestinal absorption. The relationship between hyperlipidemia (hyperglyceridemia) and oxidative damage and/or the antioxidant status is already well established [15]. Consumption of a meal rich in lipid and carbohydrate levels leads to an overall increase in oxidative stress, and thus, an increased risk for atherosclerosis and related disorders [16].

Among different endogenous biomolecules, the structure of low-density lipoprotein (LDL) molecule is one of the most prominent targets for post meal oxidative modification by the metabolic system. In a model proposed for atherosclerosis [17], it has been hypothesized that at the post meal digestion state, poor catabolic breakdown of chylomicron remnants results in an accumulation of triglyceride-rich lipoproteins. When the condition persists for a considerable period of time, it contributes to vascular injury and finally leads to initiation of atherosclerosis. The condition is further aggravated in case the diet consumed is fat rich and requires prolonged metabolic processing during which levels of circulating chylomicron remnants remain high and may lead to coronary artery disease progression [18].

Various recent studies have specified that the oxidative modification of LDL, endothelial dysfunction, and inflammation are chiefly involved in the pathogenesis of atherosclerosis [19, 20]. LDLs, if partially oxidized (oxLDL), usually remain circulating in the plasma, whereas completely oxidized LDLs get deposited in the intimal wall of the blood vessel, leading to endothelial dysfunction. Functionally disturbed endothelial cells communicate through monocyte chemotactic protein-1 (MCP-1), intercellular adhesion molecules (ICAMs), and selectins to recruit the circulating monocytes to remove the oxidized LDL moieties and restore the endothelial physiology. Selectins (P, E and L) are involved in the rolling and tethering of leukocytes on the vascular wall. ICAMs and vascular cell adhesion molecules (VCAM-1), as well as some of the integrins induce firm adhesion of inflammatory cells at the vascular surface, whereas platelet endothelial cellular adhesion molecules participate in lodging of cells from the circulating blood into the vessel wall and underlying tissue [21]. The complete process leads to the formation of fatty streaks, foam cells, and fibrous plaques [22]. Once atherosclerotic plaques come into existence, they develop into an ongoing production of inflammation, cell death, and reformation on the inside of the blood vessels. The local immune responses maintain the inflammatory milieu making

the conditions faultier and attract more immune cells, creating an expanding disarray as time passes by. Eventually this entire load becomes large enough to block a major blood vessel or gets unstable, and may break off and disastrously block a blood vessel elsewhere in the body.

In case of any interference in the patency of the blood vessel, the vessel undergoes dilatation and maintains the blood flow. The dilation of vessels is largely mediated by nitric oxide (NO), and the other factors include prostacyclin and endothelium-derived hyperpolarizing factor (EDHF). Increased levels of cholesterol in the blood causes endothelial dysfunction chiefly due to impaired NO production. Impaired NO synthase activity may result from aberrant signalling of NO synthase in cells containing elevated cholesterol either through compromised post-translational alteration of the enzyme and related signalling proteins or by downregulation of proteins associated with cholesterol [23].

The proinflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) [24–26] induce the synthesis of C-reactive protein (CRP) in the liver, which is a non-specific marker of inflammation. CRP is a key factor in the acute-phase response [24, 27, 28], and is regarded as a primary biomarker for cardiovascular health risk. It also plays a primary role in the pathogenesis of both malnutrition and atherosclerosis [29]. A new proinflammatory cytokine, IL-18, has also been found to promote experimental atherosclerosis and plaque vulnerability [30]. Moreover, autoantibodies are produced in response to the modified LDLs which circulate in the bloodstream [31–33]. The interaction between the generated anti-LDL autoantibodies and the lipoprotein results in the formation of LDL-containing immune complexes which can be detected in the circulation [34, 35] and can serve as a trigger for further defensive inflammatory processes.

4. DIETARY ANTIOXIDANTS AS FUNCTIONAL FOODS: REMEDY FOR PROPHYLAXIS AND CONTROL OF CARDIOVASCULAR DISEASES

The term "dietary antioxidants" refers to low-molecular-weight compounds which are routinely included in diet and are capable of scavenging ROS directly. Such molecules consist of tocopherols, ascorbate, carotenoids, thiols, polyphenols, and other micronutrients (e.g., selenium-containing amino acids). Atherosclerosis development as well as regression is a long term process; therefore, dietary products carry a tremendous potential in its treatment and prophylaxis. Dietary antioxidants are thought to be responsible, at least in part, for the beneficial effects of diets rich in fruits and vegetables, recommended in a worldwide campaign of disease prevention. Since oxidative stress plays a prominent role in immune system activation, antioxidant compounds like polyphenols, carotenoids, and vitamin C (e.g., citrus, tomatoes, berries, carrots, and green vegetables), lower the release of inflammatory mediators and thus, the associated risk for chronic diseases. Epidemiologically, an increased intake of antioxidant rich diet is associated with a reduced chronic inflammatory state and hence, a lower incidence for degenerative diseases [36]. Dietary practices to minimize inflammatory stimuli and hence the CVD risks include fat rich in mono- and polyunsaturated fatty acids and omega-3 fatty acids, soluble fiber, and phytosterols to reduce cholesterol as well as lower the release of inflammatory mediators. It also needs low sodium and high potassium, polyphenols as antioxidants, and vitamins (e.g., folic acid, vitamin B6 and vitamin B12) as essential cofactors [4]. Synthetic antioxidants such as butylated hydroxytoluene and butylated hydroxyanisole have lately been reported to be hazardous for human health [37] and are discouraged. Medicinal plants and edible vegetables taxonomically belonging to leguminosae (rich in isoflavones) and labiatae (rich in polyphenols) are rich in antioxidants to inhibit LDL oxidation. Moreover, many antioxidants (water-soluble flavones, isoflavones, and polyphenols) inhibiting LDL oxidation are also capable of inhibiting oxLDL-induced endothelial injuries [38].

Functional foods are foods that, by virtue of physiologically active food components, provide health benefits beyond basic nutrition, i.e., providing prophylaxis against chronic diseases besides providing traditional sustenance. Many Indian herbs are well recognized for immune-modulating activities, alleviating stress and the associated chronic inflammation, and have health promotion benefits. Today, functional foods' market is over $16 billion and is growing annually at a rate of 12% for the past 10 years. There exists a tremendous scope for the devel-

opment of functional foods to prevent health problems [39, 40]. In the present scenario, biotechnology has further paved way for the development of designer food components as per area and local requirements [41]. The use of probiotics and medicinal herbs in eggs [42] and milk production [43] has been well described for human wellbeing. Human beings require 22 essential amino acids for building body proteins. *Aloe vera* gel provides 20 of these amino acids including those which cannot be produced in the human body. Aloe has been well accepted as an immunostimulant, detoxifing (for plant toxins, and alcohol and drug overdose), antioxidative, antiviral (against herpes), bactericidal, fungicidal, anti-inflammatory, analgesic, laxative, and antidiabetic agent, and improves perception. Several Indian foods such as fenugreek, garlic, rosemary, and phytosterols have been used for ages to curtail the cholesterol in the body. A diet rich in high oleic acid—sunflower oil favorably alters low-density lipoprotein, cholesterol, triglycerides, and factor VII coagulant activity while omega-3 fatty acids improve lipid profile and reduce CVD risk.

5. SCOPE OF CARDIOVASCULAR ORIENTED FUNCTIONAL FOOD DEVELOPMENT

Development of quality functional foods from the existing sources has always been a challenge in modern era. The use of herbs and dietary supplements in combination, in addition to health benefits, can potentially increase the risk of adverse events experienced by the patients [44]. For that, continuous quality monitoring and screening of the functional foods for synergistic/antagonistic interactions among the herbal constituents is necessary [45]. Food safety parameters, such as shelf life and pathogens involved in food materials particularly of animal origin, are also of primary importance [46–49]. Simultaneously, the appearance of multidrug resistance (MDR) pathogens also needs to be given due attention [50]. Hence, the use of medicinal plants and their components is nowadays on a priority list [51–53]. Medicinal plants like *Ocimum sanctum* [51, 54, 55], *Sonchus asper* [56], *Terminalia chebula* and *Terminalia belerica* [57] have been reported for their antimicrobial activity.

Another aspect that requires attention in respect of functional food development is food allergy. Food allergy is relatively rare, but sometimes, it occurs as a violent reaction of the immune system to food proteins. The Food and Agriculture Organization of the United Nations includes soy in its list of the 8 most significant food allergens. Conversely, soy also has been successfully used to manage cow milk allergies in infants. Moreover, in the context of CVD, isoflavones from soy products have been reported to significantly reduce total cholesterol. As far as immunomodulation is concerned, several indigenous herbs have been shown to act as adjuvants for enhancing humoral and cellular immune responses [44]. In such conditions, possibility of synergism or antagonism between different components of functional foods in the development of an allergic reaction cannot be ruled out.

6. COMMON INDIAN HERBS AS CARDIOVASCULAR HEALTH PROMOTERS

Atherosclerosis has no precise therapeutic measure in herbal medicine. It has been portrayed as a disorder resulting from dyslipidemias, hypertension, enhanced platelet aggregation and thrombosis, and high oxidative stress [58]. Hence, in the present scenario, current therapy of atherosclerosis largely aims at reducing symptoms or affecting hemodynamic response and often does not affect the cause or course of disease, namely, the atherosclerotic lesion itself. Several Indian herbs carry such potential and can be used for health promotion of humans and their companion animals (**Figure 1**). Plants are the sources of common food ingredients such as dietary fiber, vitamins, minerals, oligosaccharides, lignins, and essential fatty acids. Many of these plants are part of our routine feeding habits. Thus, these plants not only promote general health, but also possess inherited medicinal values. The majority of spices that are used as an integral part of dietary foods have medicinal properties, and include onion, garlic, ginger, mustard, red chili, turmeric, coriander, clove, saffron, cinnamon, fenugreek, and curry leaves [53, 59] (**Figure 1**).

The common food ingredient, turmeric has anti-inflammatory benefits on par with hydrocortisone without any side effects of the latter [60]. Similarly, *Aloe vera* and ashwagandha have also been reported to have better anti-inflammatory potential as compared to 1% and 5% hydrocortisone cream, respec-

tively [61, 62]. The phytoconstituents of ginger, namely, gingerol, shogaol, and others, suppress 5-lipoxygenase or cyclooxygenase (COX) activity and in turn, inhibit the biosynthesis of prostaglandins and leukotrienes, and pro-inflammatory cytokines such as IL-1, TNF-α, and IL-8 [63, 64]. Shogaol can also down-regulate inflammatory iNOS (inducible nitric oxide synthase) and COX-2 gene expression in macrophages [65].

Cimicifuga racemosa, popularly known as black cohosh, has been shown to possess potent anti-inflammatory, anti-neoplastic, and antioxidant effects, which are altogether much helpful for a sound health [66]. *Mimosa pudica* (touch me not) is another Indian herb used as an antispasmodic, muscle relaxant, and anti-inflammatory agent. The phytochemical composition and anti-inflammatory activity of methanolic extracts of *C. racemosa* roots and *Mimosa pudica* seeds have been well studied [59] and no adverse findings have been reported. Both *C. racemosa* and *M. pudica* extracts contain flavonoids and other anti-inflammatory pharmacological constituents. Both *C. racemosa* and *M. pudica* extracts showed an anti-inflammatory effect greater than indomethacin, with the effect of *M. pudica* being more consistent across oral dosing protocols [67].

Garlic has been considered as an anti-atherosclerotic herb in indigenous medicine due to its hypolipidemic activity. Garlic has been found to elicit direct anti-atherosclerotic (therapeutic) and anti-atherogenic (preventive) effects by modulating pro-inflammatory cytokine release, reducing triglyceride, cholesteryl ester, and free cholesterol contents of cells cultured from atherosclerotic plaque, and preventing atherogenic serum-induced accumulation of the above lipids in cells cultured from grossly normal aorta [68]. In addition to garlic, hypolipidemic and antioxidant potency have also been observed in a routine food ingredient, tamarind [69, 70].

Isoflavonoids from soy protein products also significantly reduce the total cholesterol. When eaten in adequate amounts on a consistent basis, soy protein products may aid in decreasing the risk of CVD by several potential mechanisms. These include lowering blood lipid levels, improving arterial compliance, reducing LDL oxidation, decreasing plaque formation, scavenging free radicals, and inhibiting platelet aggregation. Herbs such as fenugreek, alfalfa, and chicory decrease cholesterol levels and shrink atherosclerotic plaques. Similarly, motherwort is another traditional heart tonic which is known to lower cholesterol, reduce platelet accumulation, and strengthen the heart. It also pacifies a tachycardiac heart rate especially in the presence of anxiety. Even small diet changes like cooking with more garlic and aromatic herbs instead of salt may have favorable effects. Antioxidant properties of peppers as with cayenne, augment the cardiovascular protective efficacy. Cayenne pepper, a cultivar of *Capsicum annuum*, reduces cholesterol and triglycerides and helps keep the blood flowing smoothly through veins and arteries due to the high amounts of capsaicin [71]. Capsaicin reduces inflammation by inhibiting the substance P, a contributor in the inflammatory cascade, and has been found to prolong fat oxidation during restricted feeding [72]. It augments circulation and blood flow to all major organs which facilitates oxygen and nutrient delivery.

Endothelial dysfunction is one of the major events in the development of atherosclerosis. The circulating oxidized LDL molecules get adhered to the endothelial lining leading to its thickening and ultimately, impede the blood flow. The role of stress in free radical generation and the prophylactic potential of Indian herbs in reducing the oxidative damage are already well acknowledged [73–75]. Several adaptogenic herbs like ginseng have been used for ages to reduce stress. Antioxidants like water-soluble flavones, isoflavones, and polyphenols which are capable of inhibiting LDL oxidation have been reported to reduce the oxLDL-induced endothelial injuries [38]. Lipophilic phenolic antioxidants, such as probucol, can circulate with the LDL molecules and trim down the rate of oxidation and prolong the initiation of pathology in the endothelial lining [76, 77]. The major polyphenol from *Glycyrrhiza* (licorice), glabridin, protects LDLs against oxidation both in in vitro and ex vivo conditions [78]. Another commonly used medicinal plant in the herbal regimens for the treatment of blood stasis is *Salvia miltiorrhiza* [41, 79], which is particularly rich in water-soluble polyphenols. Salvianolic acid B (Sal B), a water-soluble phenolic natural product identified from *S. miltiorrhiza*, is a very potent antioxidant to inhibit Cu^{2+}-induced LDL oxidation. Sal B, in particular, prolongs the lag in the time course of LDL oxidation without affecting the rate of LDL oxidation. The mechanism is similar to that of trolox, a water-soluble analogue of α-tocopherol, but the potency is 11.4 times higher than the latter [38].

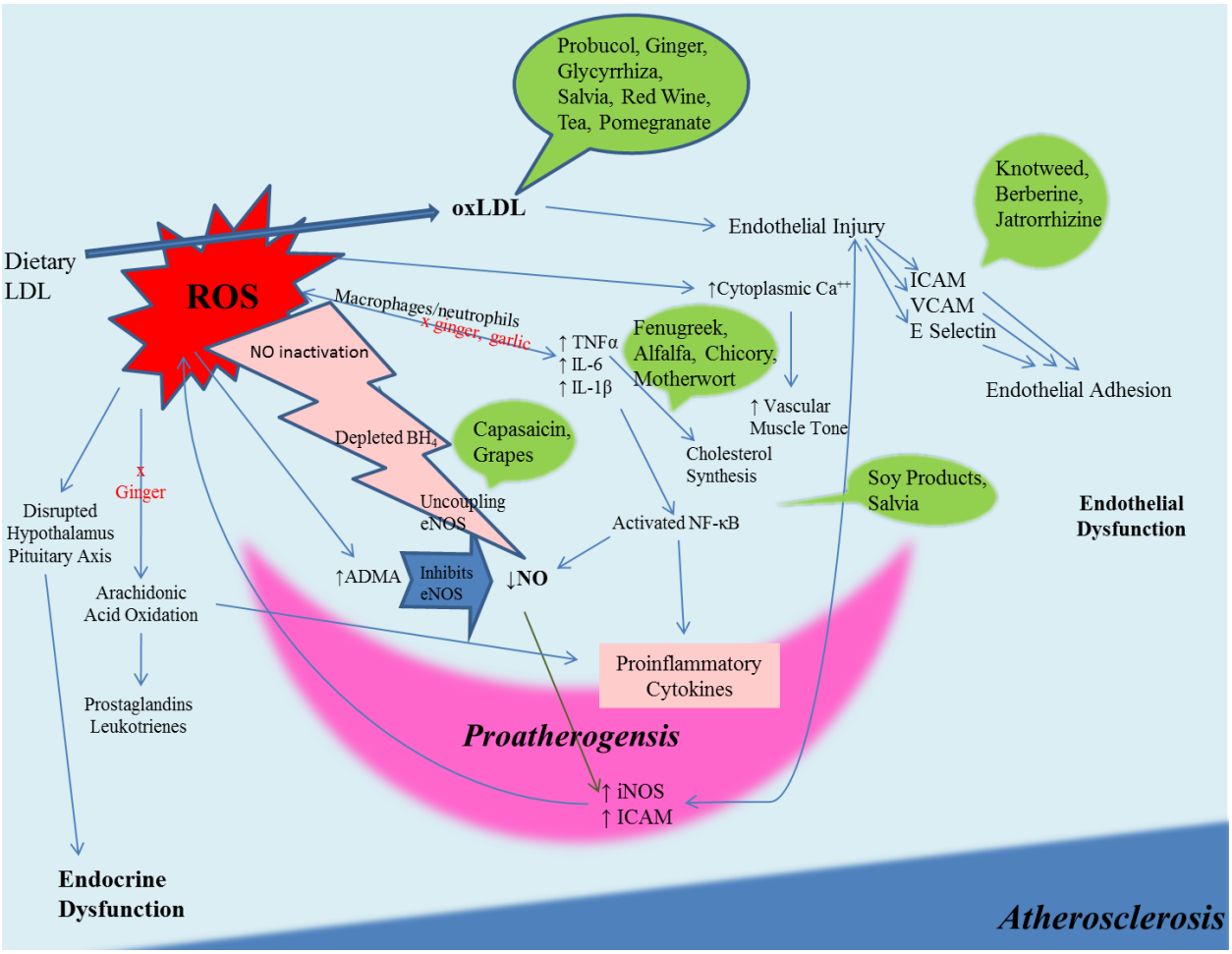

FIGURE 1. Role of nutritional stress in the induction and progression of atherosclerosis and the potential protective effects of common Indian herbs and other phytochemicals. As illustrated, oxidative and inflammatory stress are the key targets of cardiovascular protection by common Indian herbs and other phytochemicals. LDL, low-density lipoprotein; NO, nitric oxide; BH_4, tetrahydrobiopterin; ADMA, asymmetric dimethylarginine; ICAM, intercellular adhesion molecules; VCAM, vascular cell adhesion molecule.

In addition to endothelial dysfunction, formation of foam cells and fatty streaks in the subendothelial space is also noticed during early phase of atherosclerosis as an end result of macrophages engulfing the oxLDL molecules. Therefore, inhibition of the uptake of oxLDL by macrophages may also bear some therapeutic value [22]. Ganodermic acid S, an oxygenated triterpene from the medicinal fungus *Ganoderma lucidum* [80], may be successfully employed to inhibit the scavenging activity of macrophages [81]. Obstructing the expression of ICAMs with an aqueous ethanolic extract of *S. miltiorrhiza* and Sal B, as observed in TNF-α-treated cultured human aortic endothelial cells, may also be explored as another plausible target to slow down the development of atherosclerosis in its early stage [38].

In indigenous medicine, various herbs are well acknowledged for cardiovascular prophylaxis including fenugreek, angelica, arjun, astragalus, broom, hawthorn, horehound, and olives. Fenugreek seeds contain 50% dietary fiber by weight, more than half of which is soluble fiber and is responsible for hypo-

glycemic and antihypercholesterolemic benefits offered by these seeds. Moreover, the soluble fiber found in fenugreek seeds reduces the rate of reabsorption of the bile, which indirectly stimulates the liver to manufacture more bile. To increase bile production, the liver needs to use LDL cholesterol and thus, leads to a decrease in cholesterol over time, improving cholesterol status and overall health. Mint leaves, flaxseeds, and arjuna bark are well recognized for their antioxidant, anti-inflammatory, and immunomodulatory properties.

Several routinely consumed vegetables also have a proven role in regulating the cardiovascular functions. The hypocholesterolemic effect of eggplant has been well documented in addition to its rich content of iron, calcium, potassium, phosphorus, and vitamin B complex [82, 83]. Broccoli is a good source of quercetin, sulforaphane, and polyphenolic antioxidants, and may offer help in reducing cholesterol and regulating insulin [84–86]. Carrot, usually eaten raw or as a cooked vegetable, may be artery protecting, immunomodulating, and hypocholesterolemic [87, 88]. The lycopene and β-carotene content of tomatoes may also be helpful in the prevention of arterial diseases [89]. Similarly, beans may be helpful in the regulation of blood sugar and cholesterol levels to an appreciable extent [90–92].

Angelica possesses at least 14 anti-arrhythmic compounds whose action is comparable to popular calcium channel blockers. Hawthorn is a supreme cardiovascular supplement. Hawthorn berries containing flavonoids such as quercetin and oligomeric procyanidins are especially helpful in combating heart disease, high blood pressure, palpitations, and elevated cholesterol levels [93]. They improve the heart muscle's metabolism and have a marked impact on angina pectoris, arteriosclerosis, hypertension, and the fluid buildup of congestive heart failure. Grapes also host a large range of phytomedicinal compounds similar to hawthorn berries that relieve pain, reduce inflammation, and protect the cardiovascular system from free radial damage. Resveratrol supplementation can induce metabolic changes in obesity, mimicking the effects of calorie restriction. Arjun (*Terminalia arjuna*) improves the cardiac muscle function, thereby improving the pumping activity of the heart [58]. Astragalus is recommended along with *Codonopisis pilosula* to reinforce the heart in traditional Chinese medicine. Scotch broom flowers are approved for oral use for stabilizing irregular heart rhythm (arrhythmias), tachycardia, peripheral edema, pulmonary edema, congestive heart failure, cardiomyopathy, and hypotension. The flowers contain small amounts of the alkaloid, sparteine which may affect the electrical conductivity of heart muscle, similar to type 1A antiarrhythmic drugs such as quinidine. These potential properties of scotch broom may also prove to be risky in individuals taking cardiac medications [85]. Horehound has a historical reputation for calming a nervous heart [94]. The phytoconstituents of horehound, namely, marrubiin and marrubinic acid, are well known expectorants. These two compounds also help in stabilizing the cardiac rhythm.

In addition to the herbs acting directly on the cardiovascular functioning, the deterioration of such herbal ingredients in the functional foods also needs to be avoided. Rosemary leaves have been shown to improve the shelf life and heat stability of omega 3-rich oil content of the food, which is prone to rancidity. Aqueous extract of rosemary leaves has been shown to cause such effects as powerful inhibition of lipid peroxidation, stimulation of the synthesis of cellular antioxidants, decrease of the inflammatory response, and reduction of the apoptotic index, as well as improvement of the blood lipid profile [95, 96]. Evidence hints that rosemary or its constituents may have an antithrombotic ("blood thinning") activity [97] which may again be of cardiac benefit. Similarly, olive oil may be considered a major protective component of the Mediterranean diet for stroke. Scientific evidence suggests that eating about 2 tablespoons (23 grams) of olive oil daily may reduce the risk of coronary heart disease due to the monounsaturated fat in olive oil.

Herb-herb combinations have been used in Chinese medicine practice for thousands of years, yet scientific evidence of their therapeutic benefits is lacking. Due to the presence of multiple components in the herbal products, the effects arising from herb-herb or herb-drug interactions are often unpredictable and complicated. Various types of pharmacokinetic and pharmacodynamic interactions from herb-drug combinations have been well described and documented in the recent literature [98–101]. On the other hand, scanty information is available in the literature on herb-herb interactions, although herb-herb combinations have been used and documented as a desirable therapeutic approach in traditional medicine for centuries.

7. FUTURE RESEARCH PROSPECTS

Today, the food industry is dedicating scientific advancements as well as huge capital to producing foods with functional (medicinal) properties in an attempt to promote the public health. The scientific research in functional foods is increasingly powered by technological insights available from other disciplines, such as bioinformatics, pharmacology, proteomics, and genomics. Diets rich in mono- and polyunsaturated fatty acids, omega-3 fatty acids, and soluble fiber along with specific indigenous herbal inputs are being tailor-made to assist the body to curtail inflammatory incentives and the resulting CVD risks imposed by the modern lifestyle. Polyphenols can be excellent antioxidants, which together with vitamins such as folic acid, vitamin B6, and vitamin B12 may be supplemented to stimulate the overall vigor of the health. In addition to antioxidants, the herbal phytoconstituents such as sterols are being explored to reduce cholesterol levels, decrease the release of inflammatory mediators, lower sodium, and increase potassium. In contrast to their benefits, the use of herbs and dietary supplements in combination can potentially increase the risk of adverse health events, and thus proper care and scientific scrutiny are a must before the herbs can be employed for meeting the prophylactic or therapeutic targets. Thus, it may be finally concluded that the development of a functional food with appropriate amounts of several herbal dietary components will certainly lead to reduced risk of developing CVD in humans and the companion animals, but the antigenicity, efficacy, and safety of the final functional foods will need to be reassessed exhaustively.

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