Role of Dietary Supplements in Cardiovascular Diseases

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Abstract

Cardiovascular diseases (CVDs), whether congenital or acquired, are considered as a leading cause of death worldwide. Acquired CVDs are greatly correlated to dietary and other lifestyle factors including inadequate nutrition style, exposure to oxidative stress and lack of exercise. In fact, CVDs can be easily prevented and/or controlled, as advised by physicians, through quit of smoking, consumption of diet rich in polyunsaturated fatty acids, control of blood pressure, increase in physical activity, and maintenance of weight within normal limits.

In addition, certain functional foods and dietary supplements are reported to contain diverse physiologically active components with established potential in the management and/or prevention of CVDs, especially those acquired. The present chapter is intended to survey the beneficial role of these products and their individual ingredients with special emphasis on their chemical composition and mode/mechanism of action.

The role of dietary plant metabolites, viz. polyphenols, phytosterols and phytostanols, terpenoids and saponins as cardioprotective, are

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separately overviewed in this chapter. Besides, examples of commonly used herbs and herbal products, claimed to reduce CVD-risk incidence and suggested for incorporation in daily diets, are also mentioned.

1. Introduction

Plants have formed the basis of health-care throughout the world since the dawn of human civilization, and are still widely used and of great importance in international trade. The famous Hippocratic quotation “Let thy food be thy medicine and thy medicine be thy food” is now supported by numerous scientific data concerned with the beneficial role of nutrition in health improvement. On the other hand, several “lifestyle diseases”, sometimes also called “diseases of civilization” are closely associated to change in lifestyles, especially in food habits due to the tremendous increase of junk food consumption. Nutritional deficiencies in such cases are mainly referred to either generation of undesirable ingredients during food processing or incorporation of harmful food additives.

The close correlation between dietary and other lifestyle factors and specific diseases has been the subject of numerous investigations. In this respect, cardiovascular diseases (CVDs) have attracted special attention due to the continuous exposure of vessel walls to deleterious dietary metabolites. This stimulated the performance of multiple researches to explore the “protective” action of plant-derived foods and beverages with the aim to provide safe “nutritional therapies” for prevention and improvement of CVDs.

CVDs indicate a group of disorders of the heart and blood vessels including coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism, in addition to heart attacks and strokes. One of the most important behavioral risk factor of CVDs is unhealthy diet rich in fat, sugar and salt. At least, three quarters of the world’s death from CVDs occur in low- and middle-income countries due to lack of health-care programs for early detection of CVDs; in addition, the treatment of these diseases constitutes a heavy economic burden in these countries. According to the latest WHO estimate, approximately 17.5 million people died out of CVDs in 2012, representing 31% of all...
global deaths. Out of these deaths, 7.4 million occurred secondary to coronary heart disease and 6.7 million because of stroke. It is expected that by 2020, CVDs will be the major cause of morbidity and mortality in most developing nations around the globe. Approximately 25–40% of deaths in many Arab countries are due to CVDs; in Egypt, CVDs are the leading cause of death with around 27% of the population suffering from hypertension, and almost 20% from hypercholesterolemia.

The intake of a “Mediterranean Diet” rich in fruits, vegetables and dietary fibers and supplemented with olive oil and nuts has been found to reduce the incidence of major cardiovascular events suggesting that its natural antioxidant components are responsible for this action. These findings afford evidence that diet is one of the most important lifestyle modifications that can provide a beneficial approach in prevention and improvement of CVDs. The terms “nutraceuticals”, “functional foods” and “food or dietary supplements” are increasingly used to designate food or food-derived ingredients that demonstrate physiological benefits for health promotion. Definitions have been proposed to characterize these closely related products, which are supposed to exert their cardioprotective activity through lipid lowering effects, antioxidant actions and/or decreased homocysteine levels.

2. Health Promoting Foods and Food-Derived Products

2.1. Nutraceuticals versus functional foods

The term “nutraceutical”, a combination of the two words “nutrition” and “pharmaceutical”, was first coined in 1989 by Stephen DeFelice, the founder and chairman of the Foundation for Innovation in Medicine (FIM) to designate “a food (or part of a food) that provides medical or health benefits, including disease prevention and/or treatment”. However, according to Vanessa, “this term as frequently used in marketing still have no regulatory definition”. Yet, earlier attempts have been made to define “functional food” and “nutraceutical”.

A food is said to be considered as “functional food” if either “consumed as part of a normal diet and delivering one or more physiologically active ingredients that may enhance health within the food matrix” or “cooked
or prepared using scientific intelligence with or without knowledge of how or why it is being used.”

The term is assumed, as well, to designate “a food with special health functions but which is not used for therapeutic purposes.” In all cases, this food is supposed to provide the body with the required amount of vitamins, fats, proteins, carbohydrates, etc. needed for its healthy survival.

On the other hand, a “nutraceutical” is defined as “a diet supplement that delivers a concentrated form of a biologically active component of food in a non-food matrix to enhance health” or as “a functional food that helps in the prevention and/or treatment of disease(s) and/or disorder(s) other than anemia.” Nowadays, “nutraceuticals” are commonly defined as “natural health products derived from foods and supplied in different pharmaceutical forms, such as pills, capsules or liquids.” Nutraceuticals may include fortified dairy products (e.g. milk) and citrus fruits (e.g. orange juice). The fact that the management of anemia has been considered as a distinction between the two terms “functional food” and “nutraceutical” suggest that a functional food for a consumer could be regarded as a nutraceutical for another.

2.2. Food or dietary supplements and prebiotics

2.2.1. Food or dietary supplements

According to the “Dietary Supplement Health and Education Act,” a “dietary supplement” is defined as “a product (other than tobacco) that includes one or more dietary ingredients viz., a vitamin, a mineral, a herb (or other botanical), an amino acid, and any other substance intended to supplement the diet by increasing total dietary intake. It may also contain a concentrate, an extract, a metabolite, a constituent or a combination of any of the above but it should be devoid of human tissue and pathogenic bacteria.” Moreover, dietary supplements are supplied, similar to nutraceuticals, in the form of pills, capsules, tablets, or liquids; nevertheless, they constitute a special category of food and are not considered as drugs.

They currently play an important role in the US market alongside nutraceuticals and functional foods, and comprise vitamins, minerals, herbs, and botanicals (including extracts), animal extracts, amino acids, proteins,
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concentrates, metabolites and constituents, teas and miscellaneous products; yet, external patches and topical products, mouthwashes and rinses, sublingual, nasal and inhaled products, injections and suppositories are not designated as dietary supplements.

2.2.2. Prebiotics

This term designates a special type of dietary supplement of microbial origin. A prebiotic is classically defined as “a viable microbial dietary supplement that beneficially affects the host through its effects in the intestinal tract”. However, this definition was initially intended for use with animal feed products. On the other hand, the following definitions have been proposed for human consumption “a live microbial food ingredient that is beneficial to health” or “a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon.”

2.3. Nutrition labelling and health claims

Nutrition labelling and health claims should be clearly specified for all the aforementioned products viz., functional foods, nutraceuticals and dietary supplements. Nutrition labelling provides a list of the quantified nutritive components, while health claims include both “generic health claims” i.e. the scientifically-evidenced physiological potentialities in prevention and/or improvement of health disorders, and “innovative health claims” i.e. those of still not well-established disease-risk reducing properties.

2.4. Risks and side effects of dietary supplements

Despite their various health benefits, dietary supplements like drugs may have risks and side effects. In most cases, the deficiency of clinical investigations that ascertain the safety of dietary supplements and similar products constitutes a major drawback in human consumption. Most dietary supplements are self-prescribed with no proof of the given health claims from any of the medical team members as physicians, nurses, or pharmacists.
The US Food and Drug Administration (FDA) started a long time ago to monitor dietary supplements safety and issued a series of reports on illness, injury, harmful effects or adverse reactions from supplements intake. For example in 2013, exposures to dietary supplements accounted for more than 100,000 calls to US poison control centers; out of these calls, more than 8,000 people were treated in health care facilities and more than 1000 cases were transferred to poison control centers with moderate to severe outcomes. These data could be underestimated because most cases who suffer from mild or even serious side effects, illnesses, or drug interactions reported neither to a poison control center nor to the manufacturer.

3. Cardiovascular Diseases (CVDs)

Cardiovascular diseases (CVDs) include all the diseases of heart and circulation; they may be either congenital or acquired. For example, heart diseases are classified into Congenital Heart Diseases (CHD) or malformations of heart structure existing since birth, and Acquired Heart Diseases (AHD) that are conditions contracted by individuals throughout life. The different types of acquired CVDs expected to be beneficially affected by consumption of dietary products are herein briefly described.

3.1. Acquired heart diseases

3.1.1. Coronary artery disease

Coronary artery disease designates the condition leading to obstruction of blood flow in blood vessels supplying the heart muscles. The symptoms are also diagnosed as “ischemic heart disease” due to development of myocardial ischemia (reduced blood flow to the heart muscle). Among factors converting coronary artery disease into coronary heart disease are coronary thrombosis (formation of blood clots), coronary spasm, and the hemodynamic (blood-flow) needs of the heart muscle. Influences within the heart muscle itself also may increase the demand for blood flow above the level available, making the myocardium vulnerable to alterations in function, contractility, and the maintenance of normal rhythm.
3.1.2. Coronary heart disease

Coronary heart disease describes all symptoms developed from an advanced coronary artery disease because of myocardial ischemia (reduced blood flow to the heart muscle), which is the main cause of death worldwide. It includes also numerous disorders, the most important being atherosclerosis that is a case of developing plaque on the walls of the arteries. This may lead to narrowing of blood vessels and decline in blood flowing with probable blood clot formation. In this case, the part of the heart muscle supplied by that artery begins to die and a heart attack or stroke will develop. The main three risk factors leading to coronary heart disease are cigarette smoking, hypercholesterolemia and hypertension.¹³

3.1.3. Angina pectoris

Angina pectoris is a chest pain or spasm resulting from inability of occluded coronary arteries to deliver sufficient oxygen supply to the heart muscle. A feeling of suffocation always accompanied the angina pain. As a result, a myocardial ischemia is developed due to the imbalance of heart muscle demand and supply.¹³

3.1.4. Heart attack (myocardial infarction)

Heart attack (myocardial infarction) is an acute condition of necrosis that occurs as a result of imbalance between coronary blood supply and myocardial demand leading to what is called coronary thrombosis or coronary occlusion.¹³ Myocardial infarction is also considered as a complex phenomenon affecting the mechanical, electrical, structural and biochemical properties of the heart.¹⁴,¹⁵

3.1.5. Rheumatic heart disease

Rheumatic heart disease is a damage to the heart muscle and valves as result of rheumatic fever produced by *Streptococcal* bacteria.¹⁶
3.1.6. Cardiac arrhythmia

Cardiac arrhythmia describes a condition in which the heartbeat becomes irregular either too slow (bradycardia), too fast (tachycardia) or irregular (abnormal heart rhythm). In such cases, the heart may not be able to pump enough blood.\(^{16}\)

3.2. Acquired vascular diseases

3.2.1. Cerebrovascular disease

Cerebrovascular disease is a disease of the blood vessels supplying blood to brain. It is also referred to as “ischemic stroke” (the most common type), and happens when a blood vessel that feeds the brain is blocked because of which brain cells begin to die. However, when the blood vessels within the brain burst, it leads to “hemorrhagic stroke” that is most likely due to hypertension.\(^{17}\)

3.2.2. Peripheral arterial disease

Peripheral arterial disease is a disease of blood vessels supplying the arms and legs.\(^{17}\)

3.2.3. Deep vein thrombosis and pulmonary embolism

This disease symptom is characterized by blood clots in the leg veins, which can dislodge and move to the heart and lungs.\(^{17}\)

3.3. Oxidative stress-induced CVDs

Oxidative stress is defined as “a disturbance in the pro-oxidant/antioxidant balance that favors oxidation”.\(^{18}\) The organs and/or systems most susceptible to oxidative damage are the brain and eye, as well as the pulmonary, circulatory and reproductive systems. Oxidative damage causes a net stress on the normal body functions and may result in developing many specific diseases.\(^{19}\) Oxidative stress has been recognized as the unifying mechanism for many cardiovascular risk factors (diabetes and obesity)\(^{20}\) and to be involved in the etiology of several chronic diseases
including CVDs, some cancers and neurodegenerative disorders.²¹
Moreover, population studies have shown that up to 80% of CVDs, 90% of type II diabetes and approximately 30% of cancers are due to generation of free radicals under pathogenic conditions that could be avoided by diet and life style changes.²²

Many free radicals existing in living systems are unstable and highly reactive, and disrupt the equilibrium of biological systems by damaging their major constituent molecules, leading eventually to cell death. These radicals can be released from NADP oxidase, xanthine oxidase, lipoxygenase, mitochondria, or the uncoupling of nitric oxide synthase in vascular cells and damage cell lipids, membranes, proteins and DNA.²³ Free radicals can also react with serum LDL and resultant oxidized LDL damages the arterial wall.¹⁹ Dietary antioxidants (both water- and lipid-soluble), comprise important components involved in the antioxidant defense system.

### 3.4. Cancer therapy-induced cardiotoxicity

Most effective cancer therapies were found to induce cardiotoxicity. This necessitates either exploitation of tissue-specific differences between cancerous tissues and the cardiomyocyte/cardiac endothelium or, more specifically, the use of safe protective products that prevent and/or control the cardiotoxic mechanisms without disrupting antitumor pathways.²⁴,²⁵

### 4. Role of Functional Dietary Ingredients as Protective in CVDs

Lifestyle factors as inadequate nutrition style, exposure to oxidative stress and lack of exercise are playing an important role in the induction of CVDs.²⁶,²⁷ CVDs can be easily prevented and/or controlled through quit of smoking, consumption of diet rich in polyunsaturated fatty acids, control of blood pressure, increase physical activity and maintenance of weight within normal limits as advised by physicians.¹³

#### 4.1. Nutrition factors

“Nutrition factors” are sorted into three main categories: dietary pattern, individual food items and food supplements.²⁶
4.1.1. Dietary pattern

The proposed adequate “dietary pattern” includes low fat and low carbohydrate diets. The consumption of a low fat diet is generally considered in all clinical guidelines to prevent CVDs especially when rich in fruits and vegetables, and to play a protective role against CVDs.28,29

4.1.1.1. Undesirable dietary effects in CVDs development

Dietary factors play a key role in the development of some human diseases including CVDs. Epidemiologic studies indicate that diets rich in fats and carbohydrates are associated with higher risk of CVDs.

4.1.1.2. Beneficial dietary effects in CVDs protection

The cardioprotective benefits of adequate healthy diets, rich in fruits and vegetables, are manifested by reduction of bad fats levels in blood, decrease in blood viscosity and risk of blood clot development thus preventing heart attack, as well as by reduction of blood vessel inflammation and damage, in addition to regulation of heartbeat. Moreover, they provide the consumer with health-promoting anti-oxidants.

4.1.2. Individual food items

Intake of “individual food items” like whole grains (wheat, rice, barley, oats, corn and wild rice), insoluble dietary fibers (lignin and cellulose) and soluble dietary fibers (mucilage, guar gum and pectin) decrease the total cholesterol and the LDL-C.26 In fact, the American Heart Association (AHA), American Dietetic Association and National Cholesterol Education Program (ATP III) guidelines include a recommendation to increase dietary soluble fiber intake.30-32

4.1.3. Dietary supplements

Among dietary supplements with established physiological potential in prevention and/or management of CVDs are soy proteins, omega-3 fatty acids, vitamins and plant fibers.
4.1.3.1. Soy proteins supplements

Substitution of dietary animal protein with vegetable protein has been recognized to be associated with a lower risk of CVDs.\textsuperscript{33,34} Investigation of the physiological effect of Soybean food supplements led to its widespread use as protective against CVDs development. Consumption of Soy nuts (25 g soy protein) led to 9.9 and 6.8 percent reduction in systolic and diastolic BP in hypertensive postmenopausal women.\textsuperscript{35} Daily intake of 30–50 g soy resulted in total cholesterol (TC), LDL-C, and triglycerides (TG) decrease by 2–9.3, 4–12.9, and 10.5 percent, respectively, with 2.4 percent increase in HDL-C.\textsuperscript{36}

\textit{Mode of action}: Soy proteins were reported to increase LDL receptor expression in human beings.\textsuperscript{37} The BP reducing effect of Soy protein is attributed to a possible angiotensin converting enzyme (ACE) inhibitory effect of the Soy peptides (its proteins hydrolytic products).\textsuperscript{35} In addition, Soy is found to decrease the lipid micellar content and lipid absorption by its fiber, isoflavone and phytoestrogen contents.\textsuperscript{38} Similar to Soy peptides, sesame and rice protein hydrolysates show their effectiveness via ACE inhibition.\textsuperscript{39,40}

4.1.3.2. Omega-3 fatty acids supplements

Long chain n-3 PUFAs like eicosapentanoic acid (EPA, 22:5) and docosahexanoic acid (DHA, 22:6) are the major bioactive components in oily fishes. Reports on benefits of omega-3 (\textit{w}-3) polyunsaturated fatty acids (PUFAs) consumption in prevention and control of CVDs are numerous. Omega-3 fatty acids were found to reduce platelet aggregation, blood viscosity, plasma levels of fibrinogen, human platelet factor 4 (H/PF4), thromboglobulin and also to increase capillary flow.\textsuperscript{41} Omega-3 PUFAs were also reported to alter eicosanoid biosynthesis thus affecting signaling and membrane fluidity that influences enzymatic reactions and receptor binding and are important for cognitive development; in addition, they directly activate transcription factors that regulate genes affecting hyperlipidemia and inflammation.\textsuperscript{29}

Clinical trials revealed that fish oil intake reduces high triglycerides at the administered doses (4 g/d of EPA and DHA).\textsuperscript{42} An average intake of 223 mg EPA plus 149 mg DHA and/or 1.9 g ALA was also reported to exert a protective effect against ventricular arrhythmia-related events in post
myocardial infarction in diabetic patients. Experimental data suggested that long chain \( \omega-3 \) PUFAs found in fish have antiarrhythmic properties, and a randomized trial revealed that dietary supplements of \( \omega-3 \) fatty acids might reduce the risk of sudden death among survivors of myocardial infarction. Whether long-chain \( n-3 \) fatty acids are also associated with the risk of sudden death in those without a history of cardiovascular disease is unknown. The Nurses’ Health Study and Physicians’ Health Study mentioned that a lower risk of CVDs and sudden death was observed upon \( \omega-3 \) PUFA intake. In addition, a rise in median level of \( \omega-3 \) fatty acid consumption resulted in a decrease in total expected mortality by 6.4%. Similarly, supplementation with 1.5 g \( \omega-3 \) fatty acids/d from fish was found to decrease heart rate by 2.1 beats/min in selected patients, thus predicting a lower risk of sudden death due to this significant issue. Furthermore, the study conducted by Mozaffarian (2008) recommended fish or fish oil consumption (1–2 servings/wk of oily fish, or approximately 250 mg/d of EPA+DHA) in order to reduce the risk of CVD by 36%; similarly an increase of 20-g/day in fish consumption led to 7% reduction in fatal CVD. The Diet and Reinfarction Trial (DART) demonstrated a 29% decrease in mortality in men post myocardial infarction, and The Kuppio Heart Study reported 44% reduction in CHD on increasing fatty fish and fiber intake. Research studies have proven that one small serving of fish/week would reduce the risk of nonfatal myocardial infarction by 27% and death from CVD by 17%. Each additional serving would decrease the risk of death by a further 3.9% and would reduce the risk of stroke by 12%. Overall, current data provide strong concordant evidence that \( \omega-3 \) PUFAs are bioactive compounds that reduce risk of cardiac death. National and international guidelines have converged on consistent recommendations for the general population to consume at least 250 mg/day of long-chain \( \omega-3 \) PUFA or at least two servings/week of oily fish.

**Mode of action:** According to Le Guennec et al. (2010), two major pathways were suggested to be involved in the cardioprotective action of \( \omega-3 \) PUFAs. Yet, these two signaling pathways appeared not exclusively responsible and might be modulated by working in harmony with other pathways. It seems that a direct effect of \( \omega-3 \) PUFAs on ion channels is unable by itself to explain their anti-arrhythmic effects. If this is true, then the electrocardiograms of people eating large amounts of fish, like the Japanese population, would be unusual, which is not. The observed effects appear to be
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consecutive to some fatty acid peroxidation leading to production of active metabolites acting against different targets including ion channels. Although first considered as bench artefacts, the study obviously revealed that ion channels are sensitive to some peroxidized products of ω-3 PUFA released under particular physiopathological conditions where the beneficial effects of ω-3 PUFA could be observed, such as against myocardial infarction. Considering that in healthy conditions, ion channel activities are normal but when an infarction occurs, a high content of ω-3 PUFA in membrane phospholipids will permit the production of bioactive peroxidized molecules inhibiting ion channels and resulting in arrhythmias. Meanwhile, the homeostasis of phosphoinositides and associated protein kinases C (PKCs) like PKCd and PKCe are different in cells having different levels of ω-3 PUFAs incorporated in phospholipids. Thus, when α1-adrenergic receptors are activated during an ischemic episode (cardiac infarction), ion channels are differently modulated. For example, it has been shown that the activation of the α1-adrenergic pathway leads to inhibition of the delayed rectified potassium current IKr through activation of PKCs. This inhibition is involved in angiotensin-II-induced arrhythmias. The reduction of PKCd and PKCe translocation and of the associated activities can prevent a pro-arrhythmic inhibition of IKr. This hypothesis was suggested to be applicable to other currents also regulated by PKCs such as IcaL.

4.1.3.3. Vitamins supplements

As previously mentioned, oxidative stress is involved in the etiology of several chronic diseases including CVDs, some cancers and neurodegenerative disorders. Supplementation with dietary antioxidant vitamins (vitamins A, C, E), thus, appeared an alternative efficient approach to overcome the deleterious effect of free radicals and reactive oxygen species in the pathophysiology of atherosclerosis. Other vitamins (like folate, vitamin B12 and vitamin B6) have shown week effect on CVDs. Although these vitamins viz., A, C and E can also become pro-oxidant when present in low concentrations and near transition metal ions.

4.1.3.3.1. Vitamin C (ascorbic acid) is considered among the well reputed vitamins defending immune system. Being an antioxidant, it can decrease endothelial injury and lipid peroxidation induced by
free-radicals which are the main causes of atherosclerotic diseases. A meta-analysis of 11 cooperative studies conducted by Law and Morris, 1998, to evaluate the effect of dietary intake of carotenoids and vitamins A and C on CVD, revealed the presence of an inverse relationship between consumption of these food supplements and CVD risks.

4.1.3.3.2 Vitamin E (tocopherols and tocotrienols) constitutes to the most powerful group of lipid-soluble antioxidants involved in prevention of lipid peroxidation and disruption of membrane integrity. Vitamin E (particularly γ-tocopherol) is found to exhibit beneficial effects on the immune system by: decreasing platelet aggregation, inhibiting oxidation of low-density lipoprotein (LDL) cholesterol and preventing formation of blood clots, the main cause of heart attacks or thromboembolism. However, epidemiologic evidence supported an inverse relation between vitamin E intake and risk of coronary artery disease. Nevertheless, this general statement is much debated today, since previous epidemiologic findings were not supported in another large, multicenter trial of patients with increased risk of coronary artery disease. There are many potential explanations for these controversial studies, and the use of the most appropriate form and/or dose of vitamin E, essential for antioxidative activity, was recommended. Such as carotenoids (Vitamin A precursors), the controversy observed in the expected results, may be referred to the absence of certain nutrient components, which potentiate the action of α-tocopherol and are normally present in the food while absent in the dietary supplement.

4.1.3.4. Plant fibers supplements

Plant fibers are commonly described as those plant parts, which when ingested, are resistant to the action of human digestive enzymes. They are classified as ‘water-soluble’ and ‘water-insoluble’ fibers based on their water solubility. Water-soluble fibers are found in oats, psyllium, pectin, flaxseed, barley, and guar gum. Water-insoluble fibers comprise cellulose, hemicellulose, lignin, and rice and wheat brans. Fiber-rich diets were found to be associated with reduced CVDs risk. Ingestion of soluble fibers 2–10 g/day were reported to produce 5–7% reduction in LDL-C. A 12% and 19% reduction in risk for coronary events and coronary deaths was observed for each 10-g/day increment in dietary fiber;
effect was reported to be independent of the type of soluble fiber. Moreover, a dose-response relationship was noticed, with an absolute lowering of LDL-C by 1.12 mg/dl/g. Reduction in LDL-C following consumption of dietary fibers was found to be similar to that resulting from doubling the dose of statins (approximately 6%).

Mode of action: The physiological benefits of fibers largely depend upon their physical characteristics, namely, the molecular design and solubility. Soluble fibers physically bind to bile acids during the intraluminal formation of micelles and entrap cholesterol resulting in lowering cholesterol absorption. This leads to increased bile acid synthesis, reduced hepatic cholesterol, upregulated LDL receptors, and increased LDL clearance. They also increase intraluminal viscosity and slow macronutrient absorption and increase satiety leading to lower energy intake. Insoluble fibers have no effect on LDL-C, unless they replace foods supplying saturated fats and cholesterol.

5. Role of Dietary Phytochemicals in CVD Management

5.1. Plant polyphenols

Interest in dietary phenolics, especially flavonoids, has greatly increased owing to their antioxidant capacity and possible beneficial implications in human health promotion. Polyphenols range from simple phenolic molecules to highly polymerized compounds. Dietary polyphenols include flavonoids, stilbenes, anthocyanins, proanthocyanidins, tannins and curcuminoids; these are assumed to provide the health-promoting benefits associated with the Mediterranean dietary style.

Polyphenols are included in treatment and prevention of cancer, CVDs and other pathological disorders; they have been found to alter cellular metabolism and signaling, which is consistent with reducing the risk of certain CVDs.

5.1.1. Flavonoids

Flavonoids (Fig. 1) occur in appreciable amounts in dietary plants such as onion, endives, cruciferous vegetables, black grapes, red wine, grapefruits, apples, cherries and berries. Plant flavonoids are available in different
forms, either free or in glycosidic combination; they include flavones (as apigenin in chamomile, and ginkgo-flavonglycosides in ginkgo), flavanones (as hesperidin in citrus fruits and silybin in milk thistle), and flavonols (as quercetin in tea, kaempferol and rutin in grapefruit, and rutin in buckwheat).

Flavonoids play an important role in management of CVDs by blocking the AC that raises blood pressure. They prevent platelet stickiness and hence platelet aggregation by blocking the “suicide” enzyme cyclooxygenase that breaks down prostaglandins. Flavonoids also protect the vascular system and strengthen the tiny capillaries that carry oxygen and essential nutrients to all cells.\textsuperscript{29, 81, 82} The effects of cocoa flavanols ingestion and regular exercise in overweight and obese adults were explored.\textsuperscript{83} This study confirmed that as compared to low-flavanol cocoa, the high-flavanol samples acutely increased flow mediated dilation (FMD) by 2.4\% (P<0.01) and chronically (over 12 weeks; P<0.01) by 1.6\%. Furthermore, flavanol-rich cocoa intake was found to reduce diastolic blood pressure by 1.6 mmHg and mean arterial blood pressure by 1.2 mm Hg (P<0.05). Meanwhile, short- as well as long-term black tea
consumption reversed endothelial vasomotor dysfunction in patients with coronary artery disease due to their flavonol content. The mechanisms by which flavanols mediate their vascular effects are not fully understood. However, as supported by clinical data, animal and *in-vitro* studies, short-term effects of flavonoids were related to an increase in nitric oxide synthase (NOS) activity. The precise mechanism and biological target structure(s) or receptor(s) have not yet been identified *in-vivo*. Besides direct effects on NOS, inhibitory effects on pathways that may negatively affect NOS activity including NADPH oxidase, ACE, ADMA, and endothelin-1 have been proposed to be affected by flavanols. Oral administration either of flavanol-rich food extracts or of the flavanol monomer catechin to rats led to: increased acetylcholine NOS-dependent vasodilation, NO production, and decreased superoxide (O$_2^-$) production of aortic rings isolated from these animals along with a significant decrease in blood pressure. These results were, later on, confirmed by Ramirez-Sanchez, 2010 who proved that nano-micromolar concentrations of (-)-epicatechin acutely stimulate endothelial nitric oxide synthase (eNOS) activity in human coronary endothelial cells and a membrane bound acceptor was proposed. Moreover, (-)-epicatechin, as well as selected metabolites of cocoa flavanols inhibited the expression of arginase-2 in cultured endothelial cells. The effect of flavanols on arginase was also demonstrated *in vivo* providing evidence that a flavanol-rich intervention can result in an inhibition of arginase activity in human red blood cells and rat kidney *ex-vivo*; these data suggested that flavanols possess the potential to increase NOS activity by increasing the availability of the substrate L-arginine. Notably, mono-methylated flavanol metabolites were shown to enhance NO bioactivity by attenuating its degradation via O$_2$.

In a cell culture model, Schewe *et al.*, 2008 reported that 3-O-methyl-epicatechin, a bioactive metabolite of epicatechin, inhibited NADPH oxidase, thus reducing O$_2$ generation through this system. The authors reported that, under these conditions, there was an increase in steady-state NO levels as indicated by DAF-2DA fluorescence; in addition, the methylation of epicatechin in endothelial cells was found essential for inhibition of angiotensine II-mediated increase in NADPH oxidase dependent O$_2$ formation. However, this mechanism has yet to be established *in-vivo*.
Endothelins (ETs), a family of vasoactive peptides, are rapidly produced by endothelial cells in response to tissue injury and play a major role in vascular dysfunction and vascular disease.\textsuperscript{90, 91} Although (−)-epicatechin did not inhibit ET-1 synthesis \emph{in vitro}, oral administration of epicatechin lowered ET-1 levels along with increasing NO species in healthy human subjects. In accordance with reported data confirming that aortic rings do not dilate in presence of flavanol monomers, the relatively discrepant results from \emph{in vitro} and \emph{in vivo} systems demonstrated that flavanol metabolites, rather than the parent molecule, trigger many of the critical biological activities that are pertinent with respect to vascular health.\textsuperscript{85, 92}

Many of the biological activities of flavonoids have been attributed to their antioxidant properties and free radical scavenging capabilities. In fact, one of the most actively studied properties of flavonoids is their protection against oxidative stress.\textsuperscript{76, 93, 94} For example, flavonoids are ideal scavengers of peroxyl radicals due to their favorable reduction potentials relative to alkyl peroxyl radicals and thus, in principle, they are effective inhibitors of lipid peroxidation. Of particular importance is the hydrogen (electron) donating ability of a flavonoid molecule which acts to scavenge a reactive radical species, and is primarily associated with the presence of a B-ring catechol group (dihydroxylated B-ring).\textsuperscript{75}

5.1.2. \textit{Anthocyanins}

Together with catechins and proanthocyanidins, anthocyanins and their oxidation products are the most abundant flavonoids in the human diet. They are found in certain varieties of grains such as some types of pigmented rice (e.g. black rice) and maize (purple corn), and root and leafy vegetables like aubergine, red cabbage, red onions and radishes, beans; but they are especially widely distributed in red fruits including berries, red grapes, cherries and plums. The six most common anthocyanidins present in foods are pelargonidin, delphinidin, cyanidin, petunidin, peonidin, and malvidin; these mostly occur as C3-monoglycosides with glucose, fructose, galactose, xylose, arabinose or rhamnose as sugar moieties.\textsuperscript{95}

Anthocyanins are rapidly absorbed from both the stomach and small intestine,\textsuperscript{96} and appear in blood circulation and urine as intact, methylated, glucuronide derivatives and/or sulfoconjugated forms.\textsuperscript{97, 98}
Mode of action: The beneficial effects of anthocyanins on the established biomarkers of CVD risk such as NO, inflammation, and endothelial dysfunction were supported by mechanistic studies. The role of anthocyanins in CVDs prevention was found strongly linked to protection against oxidative stress. Several mechanisms of action have been proposed to elucidate their effect on the cardiovascular system. Relatively low-dose anthocyanin interventions with patients clinically diagnosed with vascular diseases have been associated with significant reductions in ischemia, blood pressure, lipid levels, and inflammatory status. Commercial grape juice (10 mL/kg) has been shown to significantly inhibit platelet activity and experimental coronary thrombosis in vivo.

5.1.3. Curcuminoids

Curcuminoids (Fig. 2) are a group of polyphenolic compounds found in the spice turmeric, including but not limited to diferuloylmethane (curcumin or curcumin I), demethoxycurcumin (curcumin II) and bisdemethoxycurcumin (curcumin III). Dietary supplements containing curcuminoids are often labelled as “Curcumin”.

Indeed, curcumin has attracted much attention due to its ability to exert beneficial effects in multiple pathological conditions. Earlier studies on curcumin have mainly focused on its effects in various forms of cancer; however, its anti-inflammatory and antioxidant properties have generated interest to explore the possibility of its use in CVD protection. Several
investigators have provided evidence suggesting the protective effects of curcumin against cardiovascular pathologies, such as atherosclerosis, vascular dysfunction, cardiac hypertrophy and heart failure.

**Mode of action:** The anti-atherosclerotic action of curcumin was found to be due to protection against inflammation and oxidation, modulation of cholesterol homeostasis and inhibition of platelet aggregation.\(^{106}\) Moreover, curcumin was found beneficial in lowering low-density lipoprotein-cholesterol (LDL-C) and raising high-density lipoprotein-cholesterol (HDL-C) while reducing lipid peroxidation. Animal studies in high fat-fed atherosclerotic rabbit model have revealed that curcumin effectively inhibits LDL oxidation and decreases cholesterol and triglycerides levels.\(^{107}\)

### 5.2. Plant phytosterols and phytostanols

Plant sterols or phytosterols (Fig. 3) are structurally and functionally similar to the animal sterol, cholesterol. Less abundant are the plant stanols or phytostanols that are completely saturated phytosterols. The major dietary sources of these compounds are vegetable oils, nuts, seeds and grains.\(^{108}\) Among phytosterols, \(\beta\)-sitosterol is the most abundant;

![Fig. 3. Representative phytosterols and phytostanols.](image-url)
others are campesterol, stigmasterol, and sitostenol. Sitosterol differs from cholesterol by an additional ethyl group at C-24 leading to its poor absorption.

The consumption of phytosterols was stated to decrease total cholesterol (TC) by 8%, Low Density Lipid (LDL) by 10% (range 6–15%) with no change in triglycerides (TGs) or High Density Lipid (HDL) in doses of 2–3 g/day in divided doses with meals. Another study revealed that around 2–3 g phytosterol/stanols/day was found to lower LDL-C by 6–15%.

Mode of action: In the gut, phytosterols were found to lower the micellar solubility of dietary and biliary cholesterol, thus decreasing the amount available for absorption and increasing bile acid secretion. They have also been reported to interact with enterocyte ATP-binding cassette transport proteins (ABCG 8 and 5) to redirect cholesterol back into the intestinal lumen to be further excreted rather than absorbed.

5.3. Plant terpenoids

Terpenoids or isoprenoids (Fig. 4) are defined as secondary plant metabolites with molecular backbones made up of isoprene (2-methylbuta-1,3-diene) units. They are classified into mono-, sesqui-, di-, tri-, tetra- and polytetrapenoids based on the number of isoprene units. Terpenoids exert significant pharmacological effects including anti-viral, anti-bacterial, anti-malarial, anti-inflammatory, inhibition of cholesterol synthesis and anti-cancer activities.

5.3.1. Iridoids

Iridoids (Fig. 4a) are a large group of phytochemicals basically of cyclopenta[c]pyran monoterpenoid structure. They are found in many plants of traditional medicinal uses including bitter tonics, sedatives, hypotensives, antipyretics, and remedies for cough and certain skin disorders. Intensive biological investigations revealed that iridoids exert a wide array of bioactivities including anti-inflammatory, antioxidant, cardiovascular, hypolipidemic, antispasmodic and immunomodulatory; in addition to neuroprotective, hepatoprotective and wound healing activities.
The richest sources of dietary iridoids are the Asian and European cornelian cherries and olive. Recently a large number of reviews reported the valuable use of olive oil on human health.\textsuperscript{116,117}

Mode of action: The angiotensin converting enzyme (ACE) inhibitory activity of \textit{Olea europea} and \textit{O. lancea} was attributed to its iridoid components.\textsuperscript{118} Among these, Oleacin\textsuperscript{119} was found to act as an irreversible ACE inhibitor with IC\textsubscript{50} of 26 \(\mu\)M. To investigate whether the alcohol or the secoiridoid part of oleacin is responsible for the ACE inhibitory activity, \(\beta\)-(3,4-dihydroxyphenyl) ethanol was synthesized. The latter was found to exert a low ACE inhibition (26\% at 0.33 mg/ml), indicating that the secoiridoid part of oleacin\textsuperscript{119} is responsible of the biological activity. Secoiridoids, such as oleuropein and its aglycone were tested. It was found that only the aglycone is active.\textsuperscript{120}

5.3.2. Triterpenoids

Triterpenoids (Fig. 4b) are a widespread and diverse group of natural products. The biosynthetic pathway towards triterpenoids proceeds by joining six isoprene units together to yield the long chain hydrocarbon squalene, which is further cyclized to different carbon structures with oleane, ursane, and lupane triterpenes being predominant. The main plant triterpenoids of the oleane group are oleanolic acid, erythrodiol and
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β-amyrin; the ursane group include ursolic acid and uvaol; and of the lupane comprise lupeol, betulin, and betulinic acid.121

Most of dietary triterpenoids are present in the peel of fruits especially in the cuticle. The apples (Malus pumila), grapevine (Vitis vinifera L.) and olive fruits are considered of the main sources of different types of triterpenoids.121

Mode of action: Inflammation remains an important cause of CVD, and is one of the mechanisms that produce heat stress and lead to decreased muscle growth,122 and subsequent mitochondrial apoptosis (programmed cell death) of cardiac myocytes thus resulting in CVD.123

Besides phenolic compounds, fruits and vegetables have been found to contain appreciable amounts of triterpenoids, which reduce or delay CVD onset124 such as risk of chronic obstructive pulmonary disease and thrombotic stroke.125 Reported data suggest a positive correlation between reduced frequencies of CVD and ingestion of natural resinous materials and plants rich in triterpenoids.126 The beneficial influence of triterpenoids from dietary fruits such as apples, grape berries, olives, tomatoes, and mangoes on inflammation and CVD has been investigated and documented.121

Fig. 4b. Representative plant-derived triterpenoids.

Oleanolic acid: $R_1 = \text{COOH}, R_2 = \text{CH}_3, R_3 = \text{H}$
Erythrodiol: $R_2 = \text{CH}_2\text{OH}, R_3 = \text{CH}_3, R_3 = \text{H}$
β-Amyrin: $R_1 = R_3 = \text{CH}_3, R_2 = \text{H}$
Ursolic acid: $R_1 = \text{COOH}, R_2 = \text{H}, R_3 = \text{CH}_3$
Uvaol: $R_1 = \text{CH}_2\text{OH}, R_2 = \text{H}, R_3 = \text{CH}_3$

β-amyrin

Lupeol: $R_1 = \text{CH}_3$
Betulin: $R_1 = \text{CH}_2\text{OH}$
Betulinic acid: $R_1 = \text{COOH}$
5.3.2.1. Apple triterpenoids

Apple peel triterpenoids (mainly ursolic acid), were reported to have anti-hypertensive effects, with capacity to inhibit platelet aggregation, and increase endothelial-dependent vasodilation. Both animal and human trials demonstrated that ingestion of apple triterpenoids significantly lowered the overall plasma cholesterol level, LDL-C, and TG concentrations.

*Mode of action:* The inhibitory mechanisms of TNF-α gene on lipase were recognized to be regulated through consumption of triterpenoids from apples, grapes, and olives fruits which might reduce the risk of myocardial ischemia and atherosclerosis. Moreover, apple peel triterpenoids were found to act through an antioxidant mechanism in plasma and serum thus reducing DNA damage, inflammation, and oxidative stress levels. In addition, ursolic acid was found to activate the mechanism regulating Mcl-1 pro-apoptotic protein and thus decreasing adverse consequences of heat stress in cardiomyocytes and to mediated anti-apoptotic and anti-oxidative activities against endoplasmic reticulum (ER) stress-associated myocardial damage.

5.3.2.2. Grape peel triterpenoids

The reputed health promoting properties of grape products is attributed to its potential anti-oxidant and anti-inflammatory property. Beside flavonoids, grape peels are rich in triterpenoids, particularly oleanolic acid (OA).

*Mode of action:* Ingestion of OA was found to reduce oxidative stress, HBP flux, and apoptosis via increasing myocardial level of Nrf2 and Nrf2 nuclear translocation. OA was also reported to confer beneficial effects in CVD prevention through a number of mechanisms that include: mediation of urinary F2-isoprostanes regulation, enhancement of superoxide production, reduction of serum cholesterol level, and decrease of LDL liability to oxidation. Moreover, OA was found to possess an anti-inflammatory cytokine profile that promotes interference with cardiac-specific antibodies generation, and prevention and treatment of EAM by conferring protective effects on cardiac cells and inflammatory cardiomyopathies. Besides, OA also increased plasma atrial natriuretic peptide (ANP) levels, a mechanism involved in cardiovascular homeostasis.
regulation. The synthetic OA derivative dh404, functioning through pathological cardiac dysfunction inhibition, reduced mortality rate caused by cardiomyocytes death and cardiac fibroblasts proliferation. In another study, the significant ability of OA to reduce plasma nitrate/nitrite level through releasing nitric oxide was established. Finally, OA was found to inhibit COX-2 enzyme and Th1 responses, which can reduce the risk of inflammation.

5.3.2.3. Olive triterpenoids

Vioque and Morris, 1961 found two triterpenic acids in the acetonic extract of the olive pomace, one of which was identified as oleanolic acid (OA) and the other defined as a dihydroxytriterpenoic acid. Later on, Bianchi et al., 1994 quantified maslinic acid together with oleanolic acid as major lipid components in the cuticle of olive fruit. Furthermore, maslinic acid has recently been quantified in edible vegetables, as table olives, spinach and eggplant, aromatic herbs like mustard and basil, legumes as chickpeas and lentils, and in lesser amounts in some fruits like mandarin and pomegranate.

Mode of action: Maslinic acid (MA) products like olive fruits significantly suppressed the expression of COX-2 and iNOS, thus exerting an anti-inflammatory effect. MA also exhibited a potential effect in oxidative stress resistance by targeting mechanisms that reduce hydrogen peroxide generation from macrophages and intracellular reactive oxygen species (ROS) level, while offering no harmful reaction as a nutraceutical.

5.3.3. Carotenoids

Carotenoids (Fig. 5) are a class of more than 600 naturally occurring tetraterpenoid pigments synthesized by plants, algae, and photosynthetic bacteria. These richly colored molecules are the sources of the yellow, orange, and red colors of many plants. Fruit and vegetables provide most of the carotenoids in the human diet. Carotenoids can be broadly classified into two classes, carotenes (α- and β-carotenes, and lycopene) and xanthophylls (β-cryptoxanthin, lutein, and zeaxanthin). Those converted in the body to retinol like carotenes and β-cryptoxanthin are provitamin A carotenoids; meanwhile others as lutein, lycopene, and zeaxanthin, which are not converted to retinol, have no vitamin A activity.
Yet, all dietary antioxidant carotenoids of both carotene and xanthophyll groups including β-carotene, lycopene, lutein, β-cryptoxanthin, zeaxanthin, and astaxanthin were found to play an important role in prevention and/or management of CVDs. They are abundant in fruits and vegetables, and are superior in action to individual synthetic carotenoids. Several studies revealed the strong correlation between dietary sources of lycopene and reduced risk of heart attacks. Lutein and zeaxanthin have been proven to inhibit the thickening of coronary artery walls and to reduce arterial inflammation, thus combating LDL-induced migration of monocytes to human artery cell walls.

5.4. Plant saponins

Saponins are biosurfactants composed of a rigid hydrophobic structure of a steroid or triterpenoid type, which is linked to one, two or three hydrophilic sugar chains. Saponins are known to possess a wide range of biological activities, such as enhancing cell membrane permeability, regulating nutrient uptake in the intestine, reducing protein digestibility, decreasing serum cholesterol among others. Saponins are found in most vegetables, beans and herbs. The best-known sources are peas, soybeans, fenugreek and licorice.

Mode of action: Two main mechanisms have been proposed to elucidate the effect of saponins in lowering of serum cholesterol. The first
mechanism suggested that saponins form insoluble complexes with cholesterol, thus inhibiting its intestinal absorption. This mechanism was supported by animal studies, which reported that dietary intake of alfalfa saponins increased the fecal cholesterol output; moreover, in-vitro model experiments demonstrated the formation of insoluble alfalfa saponin–cholesterol aggregates when cholesterol crystals are placed in contact with alfalfa saponin solutions. The second mechanism proposed that saponins form large aggregates with bile salts (BS) in the intestine thus inhibiting ideal BS reabsorption; this latter effect triggers an increased synthesis of BS from cholesterol in the liver leading to depletion of serum cholesterol. Examples of this mechanism are soya saponins, which were observed to form large mixed aggregates with BS, molecular mass >10^6 a.u., which were not absorbed by rat intestine in-vivo.162,163

6. Examples of Dietary Herbals Affecting CVD

6.1. Globe artichoke leaves

Leaves of Globe artichoke (*Cynara scolymus* L., Asteraceae/Compositae) are highly enriched in phenolic acids (up to 2%, chiefly caffeic acid, and mono- and dicaffeoylquinic acid derivatives viz., cynarin and chlorogenic acid).164 Flavonoids (0.1–1%) mainly flavone glycosides (luteolin-7-β-rutinoside or scolymoside, luteolin-7-β-D-glucoside and luteolin-4-β-D-glucoside), and volatile components with major sesquiterpenes (β-selinene and caryophyllene) were also detected.165 Among other identified constituents in the leaves are: phytosterols (β-taraxasterol), tannins, glycolic and glyceric acids, sugars, inulin and enzymes (peroxidases),165 and sesquiterpene lactones (cynaropicrin, grosheimin, and cynarotriol).166 On the other hand, the root and fully developed fruits and flowers are devoid of cynaropicrin; the highest content being reported in young leaves.164,167

Several pharmacological properties have been reported for artichoke leaf, including inhibition of cholesterol biosynthesis, hypolipidaemic,
antioxidant and hepatoprotective activity.\textsuperscript{164} The hypolipidaemic and hypocholesterolemic activities are mainly attributed to cynarin (1,5-di-O-caffeoylquinic acid).\textsuperscript{168} The inhibition of cholesterol biosynthesis, as established in rat hepatocytes cultures, is achieved in a concentration-dependent manner.\textsuperscript{169-170} This activity was referred to be partly due to Luteolin through indirect inhibition of hydroxyl methylglutaryl-CoA reductase.\textsuperscript{170}

### 6.2. Evening primrose seed oil

The fixed oil (14\%) of the seeds of Evening primrose (\textit{Oenothera biennis} L., Onagraceae) is rich in $\omega$-fatty acids namely, \textit{cis}-Linoleic acid (LA) (65–80\%), \textit{cis}-\textit{\gamma}-linolenic acid (GLA) (2–16\%), oleic acid (9\%), palmitic acid and stearic acid (7 and 3\%).\textsuperscript{164,171,172} The oil was found to decrease blood pressure and platelet aggregation in humans\textsuperscript{172} these bioactivities are attributed to its \textit{\gamma}-Linolenic acid content.

### 6.3. Rasberry leaves

Phenolics are the major components of the dried leaves of Rasberry (\textit{Rubus idaeus} L., Rosaceae). Flavonoids (0.46–1.05 up to 5\%)\textsuperscript{173} are mainly represented by quercetin and kaempferol derivatives\textsuperscript{174} including: quercetin-3-\textit{O}-\textit{\beta}-D-glucoside,\textsuperscript{175} quercetin- and kaempferol-3-\textit{O}-\textit{\beta}-D-galactosides, kaempferol-3-\textit{O}-\textit{\beta}-L-arabinopyranoside and kaempferol-3-\textit{O}-\textit{\beta}-D-(60-p-coumaroyl)-glucoside (tiliroside)\textsuperscript{176}; besides, polyphenols as
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Gallo- and ellagi-tannins amount to 2.06–6.89 and up to 10%. Volatile components (E-2-hexenal and Z-3-hexenol), glycosides of C13-norisoprenoids and vitamin C are minor.

The plant berries, as well, are rich in polyphenols namely, anthocyanins, hydrolysable tannins, sanquins H6 (a dimeric ellagitannin) and lambertin (a tetrameric ellagitannin); in addition to triperpenoids (α- and β-amyrin), sterols (stigmasterol, campesterol, cycloartenol, cholesterol) and raspberry ketone were also detected.

Aqueous extracts of raspberry leaves were reported to produce diverse pharmacological actions including smooth muscle stimulant, anticholinesterase, and antispasmodic effects. The smooth muscle stimulant fraction was more potent towards uterine muscle. Flavonoids isolated from 70% ethanol extracts of the leaves of four Russian raspberry varieties exerted antioxidant activity in vitro, when assessed in a system involving measurement of the rate of oxygen absorption during isopropylbenzene-initiated oxidation.

6.4. Tea leaves

The major constituents of tea (Camellia sinensis L., Theaceae) leaves are methylxanthine alkaloids and polyphenols. Caffeine (3–4%), theobromine and theophylline are the major alkaloids. Polyphenols mainly flavanols or catechins (epicatechin, epicatechin-3-gallate, epigallocatechin, with major epigallocatechin-3-gallate reach up to 30–40% in green tea, whereas only 3–10% in black tea. The main detected flavonols (2–4%) in green tea leaves are myricetin, quercetin and kampferol.

Black Tea was found to decrease systolic blood pressure by 2.6 mm/Hg and diastolic by 2.2 mm/Hg. In another study, participants who drank 1–2 cups of Black Tea daily had a 46% lower risk of severe aortic
atherosclerosis, a strong indicator of cardiovascular disease; meanwhile, those who drank more than 4 cups of tea per day had a 69% lower risk.

6.5. Fenugreek seeds

The seeds of Fenugreek (Trigonella foenum-graceum L., Fabaceae) are characterized by the presence of alkaloids of the pyridine-type (gentianine and trigonelline, up to 0.13%), as well as choline (0.05%); proteins and amino acids (high quantities of lysine and tryptophan); flavonoids represented by flavone (apigenin, luteolin, orientin and vitexin), and flavonols (quercetin). Saponins (0.6–1.7%) were also detected mainly glycosides of the steroidal sapogenins diosgenin and yamogenin, besides those of tigogenin, neotigogenin, gitogenin, neogitogenin, smilagenin, sarsasapogenin, yuccagenin; fenugreekine, as well as sapogenin-peptide ester involving diosgenin and yamogenin; trigofoenosides A–G (furostanol glycosides). In addition to other constituents as coumarin, lipids (5–8%), mucilaginous fibre (50%), vitamins (including nicotinic acid) and minerals.

Seeds are used as treatment of diabetes with additional lipid-modifying and anti-inflammatory and antipyretic effects. The dietary fibers (glucomannan) and steroidal saponins lead to reduced very low density lipoprotein (VLDL) production. However, the lack of substantial animal studies and human studies refutes the effectiveness of Fenugreek for management of dyslipidemia.

6.6. Flaxseed (Linseed)

Flaxseed (Linum usitatissimum L., Linaceae) is considered as oilseed crop due to its high polyunsaturated fatty acid content notably the essential ω-3 fatty acid:
α-Linolenic acid (ALA-57%), the essential ω-6 fatty acid (16%). Moreover, flaxseed is the richest source of plant lignans secoisolariciresinol digluco-side (SDG), and minor matairesinol (MAT) and pinoresinol. The seed protein (10.5% to 31%) is mainly composed of arginine, glutamic acid and aspartic acid, with lower amounts of cystine, methionine and lysine; meanwhile, the amount of dietary fibres (soluble and insoluble) reaches up to 28%; besides the cyanogenic glycosides linusatin and neolinusatin were also detected.

Several pharmacological properties have been attributed to Linseed fixed oil, especially α-linoleic acid (ALA), which was found responsible of the reduction of the 7 α-hydrolyase and acyl CoA cholesterol transferase (ACAT) levels. The oil exerted anti-inflammatory activity, increased endothelial nitric oxide synthase and improved endothelial dysfunction. The lignan components (phytoestrogens) reduced the vascular smooth muscle hypertrophy and oxidative stress, and retarded development of atherosclerosis. They also reduced TC and LDL by 5–15%, lipoprotein (α) by 14%, and TG by 36%. The Lyon Diet Trial demonstrated that intake of flax reduced CHD and total deaths by 50–70%. The daily dose recommended to produce these effects was 14 to 40 g of flax seeds.

6.7. Rice bran

Rice bran is a byproduct of the rice (Oryza sativa L., Gramineae) grain milling process to convert brown rice to white rice. Rice bran contains various bioactive constituents that exert beneficial effect on human health and may be helpful in protection against CVDs. These include: γ-oryzanol (ferulic acid esters), vitamin E (α-, γ- and δ-tocopherols, tocotrienols), α-lipoic acid (thiotic acid), phenolic acids (ferulic, caffeic and salicylic acids), phytosterols (β-sitosterol, campesterol, and stigmasterol), carotenoids (α-carotene, β-carotene, lycopene, lutein, and zeazanthin), tricin (O-methylated flavone) and phytic acid (inositol hexaphosphate). Furthermore, rice bran contains a mixture of both soluble and...
insoluble dietary fibers *viz.*, cellulose, hemicellulose, pectin, arabinoxylan, lignin, and β-glucan;\textsuperscript{210–212} essential amino acids (tryptophan, histidine, methionine, cysteine, and arginine);\textsuperscript{213} minerals (magnesium, calcium, phosphorous, manganese);\textsuperscript{214} and vitamins.\textsuperscript{214}

Compared with other cereal brans, such as corn, wheat, and oat, the lipid fraction of rice bran contains a unique ratio of vitamin E isoforms, γ-oryzanol, and β-sitosterol\textsuperscript{215} that was found to decrease TG, LDL, and triglycerides levels resulting in CVDs-risk reduction. Moreover, intensive investigations of the bioactivity of diverse compounds isolated from rice bran revealed their efficiency in prevention and control of several chronic diseases including Alzheimer and neurodegenerative disorders, treatment of malnutrition in children, and protection against mitochondrial denaration.\textsuperscript{216,217}

### 6.8. *Ispaghula seeds (Psyllium seeds)*

Psyllium seeds (*Plantago ovata* Forssk., Plantaginaceae) are characterized by the presence of: alkaloids of the monoterpene-type\textsuperscript{164} *viz.*, β-Boschniakine (indicaine), β-boschniakinic acid (plantagonine) and indicainine; in addition to mucilage (10–30%), present mainly in the seed husk, and consisting mainly of a highly branched arabinoxylan with a xylan backbone and branches of arabinose, xylose and 2-\text{O-}(galacturonic)-rhamnose moieties.\textsuperscript{164} Besides, other constituents such as: aucubin (iridoid glucoside), sugars (fructose, glucose, sucrose), plantose (trisaccharide), protein, sterols (campesterol, β-sitosterol, stigmasterol), triterpenes (α- and β-amyrin), fatty acids (e.g. linoleic, oleic, palmitic, stearic) and tannins were also detected.\textsuperscript{164}

The pharmacological actions of ispaghula seeds are mainly ascribed to its mucilage content. Ispaghula exerts a bulk laxative effect as the swelling properties of the mucilage enables to increase the stools water content and thus the peristaltic movement. In addition, its hypocholesterolemic activity was observed *via* a double blind, placebo controlled study;\textsuperscript{218} where
26 men with mild to moderate hypercholesterolemia were receiving ispaghula (3.4 g) for eight weeks (three times daily). By the end of this study, the level of serum cholesterol was reduced by 14.8% in the treated group, low-density lipoprotein (LDL) cholesterol by 20.2% and ratio of (LDL) to (HDL) by 14.8%, compared with baseline values.218

6.9. Turmeric rhizome
Turmeric rhizome (Curcuma longa L., Zingiberaceae) is rich in many bioactive constituents such as: phenolic compounds and terpenoids including diarylheptanoids (commonly known as curcuminoids), diarylpentanoids, monoterpenes, sesquiterpenes, diterpenes, triterpenoids, alkaloid, and sterols.219

In India, turmeric is widely used in management of diseases related to circulation and neurological disorders. In a natural mutant model of obesity, turmeric (at 1 and 5% of the diet) had significantly reduced cholesterol and triglyceride concentrations while increasing HDL cholesterol, within 4 weeks.220 Further evidence indicates that it reduces the oxidation of LDL, blood glucose and renal lesions in diabetes. In addition, it has been demonstrated that turmeric reduces platelet aggregation, cyclooxygenase, thromboxane, smooth muscle cell proliferation and endothelial dysfunction. Both turmeric and curcumin, due to their antioxidant and anti-inflammatory activities, have been proven to counteract several disorders such as myocardial infarctions, chronic inflammatory lung diseases, pancreatitis, inflammatory bowel diseases, neurodegenerative diseases, hepatic and lung damages as well as muscle injuries and cystic fibrosis. Curcumin was also found to impact on the process of cataractogenesis and delay galactose-induced cataracts formation in rats.220

6.10. Ginger rhizome
Constituents reported in the rhizomes of ginger (Zingiber officinale Roscoe, Zingiberaceae)221 are numerous. The major is a resin formed of
mainly gingerol (about 33%) including derivatives with a methyl side-chain,\textsuperscript{221} shogaol homologues (dehydration products of gingerols), zingerone (degradation product of gingerols), 1-dehydrogingerdione.\textsuperscript{222}

Volatile components amounted to 1–3% and are predominated by sesquiterpene hydrocarbons \textit{viz.}, \( \beta \)-bisabolene and zingiberene (major); in addition to zingiberol, zingiberenol, ar-curcumene, \( \beta \)-sesquiphellandrene, \( \beta \)-sesquiphellandrol (\textit{cis} and \textit{trans}); besides monoterpenes hydrocarbons, alcohols and aldehydes (\textit{viz.}, phellandrene, camphene, geraniol, neral, linalool, \( \alpha \)-nerol).\textsuperscript{164} In addition to some other constituents such as amino acids (arginine, aspartic acid, cysteine, glycine, isoleucine, leucine, serine, threonine and valine), protein (9%), and diterpenes (galanolactone),\textsuperscript{164} vitamins (especially niacin and vitamin A) and minerals.\textsuperscript{223}

Ginger has been used traditionally for alleviation of various human ailments such as indigestion, stomach upset, diarrhoea and nausea. Ginger rhizome is generally consumed as a fresh paste, dried powder, slices preserved in syrup, candy (crystallized ginger) or for flavoring tea. In Siddha literature, it is recommended for treatment of hypertension and diseases related with circulation.

In a placebo controlled clinical trial, coronary artery-diseased patients receiving a single dose of 10 g powdered ginger showed a significant reduction in platelet aggregation without affecting the blood lipids and blood sugar.\textsuperscript{220} Oral administration of ginger rhizome ethanol extract in a dose of (200–500 mg/Kg) to hyperlipidemic rabbits exhibited a significant lipid reduction in cholesterol, triglycerides and liproteins serum levels.\textsuperscript{224} Furthermore, an alcohol extract standardized to contain 40 mg/g gingerols, shogaols and zingerone, and 90 mg/g total polyphenols, was reported to inhibit low-density lipoprotein oxidation and to reduce the development of atherosclerosis in atherosclerotic mice, when compared with control.\textsuperscript{225} Ghayur \textit{et al.}, (2005)\textsuperscript{193} reported the hypotensive, endothelium-dependent and –independent vasodilator, cardio-suppressant and
stimulant effects of the aqueous extract of ginger. An atropine-resistant vasodilator activity was also observed from ginger phenolic constituents 6-, 8- and 10-gingerol, while 6-shogaol showed a mild vasodilator effect. The data indicate that the aqueous ginger extract lowers BP through a dual inhibitory effect mediated via stimulation of muscarinic receptors and blockade of Ca\textsuperscript{2+} channels.

6.11. Black pepper fruits

Black pepper (Piper nigrum L., Piperaceae) is one of the most useful spices. Its volatile oil consists of \(\beta\)-caryophyllene (24.24%) followed by limonene (16.88%), sabine (13.01%), \(\beta\)-bisabolene (7.69%), \(\beta\)-pinene (6.71%), \(\alpha\)-copaene (6.3%), camphene (4.75%), \(\delta\)-cadiene (2.37%), terpinen-4-ol (1.99%), tricyclene (1.73%) and \(\alpha\)-humulene (1.38%). Black pepper is characterized by the presence of the pungent piperine alkaloid.

Black pepper has an impressive antioxidant and antibacterial effect and helps with digestion and weight loss because it stimulates the breakdown of fat cells. The diverse physiological effects of piperine has been experimentally investigated; it was found to act by eliminating factors that increase fat accumulation. The methanolic extract of Piper longum exhibits a significant protection against adriamycin induced cardiotoxicity by virtue of its antioxidant and free radical scavenging capacity. Black pepper has been reported to influence lipid metabolism predominantly by mobilization of fatty acids. An in vivo study on hypolipidemic effect of black pepper in high fat diet fed rats treated with black pepper as well as piperine showed remarked decrease in the levels of cholesterol (both the free and ester cholesterol fractions), free fatty acids, phospholipids and triglycerides. Moreover, supplementation of the high fat fed rats with black pepper elevated the concentration of high density lipoprotein-cholesterol (HDL-C) and reduced the concentrations of low density lipoprotein-cholesterol (LDL-C) and very low density lipoprotein-cholesterol (VLDL-C) in the plasma as compared with the levels in unsupplemented high fat fed rats.
6.12. Cumin fruits

Cumin (Cuminum cyminum L., Apiaceae) is characterized by its volatile oil constituents: the monoterpenic hydrocarbons \( \beta \)-pinene, \( p \)-cymene and \( \gamma \)-terpinene and the terpenoid aldehydes mainly cuminic aldehyde.\(^{228}\)

Cumin was found to significantly reduce the plasma levels of cholesterol, triglycerides and phospholipids. It also decreases the activity of aspartate transaminase, alkaline phosphatase and gamma glutamyl transferase enzymes (non-specific indicators of tissue damage) and thus to be efficient in liver diseases (alcoholic liver disease, chronic hepatitis, cirrhosis, obstructive jaundice, hepatic cancer), myocardial infarction, pancreatitis and muscle-wasting diseases).\(^{229}\) The activity of phospholipases A and C (enzymes that catalyze the splitting of phospholipids into fatty acids and other lipophilic substances by the addition of water) were also decreased significantly. The results obtained indicated that cumin could decrease the lipid levels in alcohol and thermally oxidized oil-induced hepatotoxicity.\(^{229}\)

7. Conclusion

Primary health care requires the utilization of all appropriate and easily available local resources. The attention paid by health authorities and administrations to the use of medicinal plants is continuously increasing worldwide, in both undeveloped and developing countries. The production of pharmaceuticals is currently directed towards the use of raw plant materials and/or constituents to avoid the noxious side effects of conventional chemicals, especially in management of chronic diseases. Moreover, the beneficial role of nutrition in health improvement, now evidenced by multiple scientific data, greatly supports the famous Hippocratic quotation “Let thy food be thy medicine and thy medicine be thy food”.

Lifestyle diseases, also called “diseases of civilization” or “chronic health conditions”, are more common in highly industrialized countries. They
include cardiovascular diseases, some types of cancers, diabetes, and neurodegenerative diseases. They are linked to alcohol, drug and smoking abuse, as well as lack of physical activity and unhealthy food consumption. Nutritional deficiencies, in such cases, are mostly referred to either generation of undesirable ingredients during food processing or incorporation of harmful food additives. Chronic diseases are preventable diseases but require changes in lifestyle and dietary supplementation.

The influence of healthy diets in prevention and amelioration of certain chronic ailments has been the subject of numerous investigations. Studies released by the Cancer Research UK, National Cancer Institute of USA, and National University of Singapore, revealed that Asian women had a lower risk of breast cancer than those of Western countries due to consumption of large amounts of soy foods rich in phytoestrogens and isoflavonoids. Similar effects were observed with those fed with large amounts of flaxseed and was attributed to its high lignan content.

Globally, cardiovascular diseases (CVDs) are considered, nowadays, as the predominant cause of death, and place a heavy burden on countries’ economies. Over 80% of CVD deaths are reported from low- and middle-income countries being almost equal in men and women. CVDs are closely related to smoking, stress, bacterial and virus infections, in addition to environmental and nutrition factors. Healthy dietary habits appear to play a significant role in prevention and management of CVDs. In fact, the lowest death incidence from CVDs was recorded for population consuming Mediterranean diet that is rich in fruits, vegetables and olive oil; this decrease in CVD-risk has been attributed to the abundance of natural antioxidants in this type of diet. Likewise, people originating from countries that consume large amounts of spices in their foods were found less susceptible to CVDs and cancers. Dietary spices which play an important role in prevention and/or control of chronic diseases include black pepper, red chili, ginger, black cumin, fenugreek, fennel, cardamom, with turmeric being the most reputed.

This article provides an overview of the multiple researches dealing with exploration of the “protective” action of plant-derived dietary products which could be considered as safe “nutritional therapies” for prevention and improvement of CVDs. Components cited therein are recommended
to be dispensed, after appropriate clinical trials, in different forms such as "nutraceuticals", "functional foods", and "food or dietary supplements".

**Abbreviations**

omega-3 (ω-3), Acyl CoA cholesterol transferase (ACAT), angiotensin converting enzyme (ACE), American Heart Association (AHA), Acquired Heart Diseases (AHD), atrial natriuretic peptide (ANP), Adult Treatment Panel III (ATP III), bile salts (BS), Congenital Heart Diseases (CHD), Cyclooxygenase-2 (COX-2), Cardiovascular diseases (CVDs), diet and Reinfarction Trial (DART), docosahexanoic acid (DHA), Deoxyribonucleic acid (DNA), endothelial nitric oxide synthase (eNOS), eicosapentanoic acid (EPA), endoplasmic reticulum (ER), Endothelins (ETs), Food and Drug Administration (FDA), flow mediated dilation (FMD), gammalinoenic acid (GLA), human platelet factor 4 (H/PF4), high-density lipoprotein-cholesterol (HDL-C), delayed rectified potassium current (IKr), Inducible nitric oxide synthase (iNOS), Linoleic acid (LA), low-density lipoprotein-cholesterol (LDL-C), Maslinic acid (MA), matairesinol (MAT), reduced Nicotinamide adenine dinucleotide phosp (NADPH), nitric oxide synthase (NOS), oleic acid (OA), protein kinases C (PKCs), polyunsaturated fatty acids (PUFAs), reactive oxygen species (ROS), secoisolariciresinol diglucoside (SDG), total cholesterol (TC), triglycerides (TG), United State (US), very low density lipoprotein (VLDL).

**References**

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