



The Role of Nutraceuticals in Managing Cardiovascular Disease

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Abstract: Nutraceuticals can play an important part in the body's various biological processes, which help prevent various diseases and improve overall health and well-being. The underlying mechanisms of cardiovascular disease (CVD) vary depending on the specific condition. Dietary risk factors are estimated to be linked to 53% of CVD-related fatalities. Atherosclerosis, which is implicated in coronary artery disease, stroke, and peripheral artery disease, can be initiated by factors such as high blood pressure, smoking, diabetes mellitus, insufficient physical activity, obesity, elevated blood cholesterol, poor dietary habits, excessive alcohol consumption, and inadequate sleep, among other contributors. Approximately 13% of CVD deaths are attributed to high blood pressure, 9% to tobacco use, 6% to diabetes, 6% to lack of exercise, and 5% to obesity. Nutraceuticals have shown efficacy and are simple to use, making them a viable alternative for intervention. Lack of guidelines has so far restricted the use of nutraceuticals in clinical settings; this is probably due to a history of lax regulatory requirements that permit supplements to be sold on the market before thorough clinical trials are completed. The market and research on the use of nutraceuticals have recently caught up, which may permit the clinical use of supplements from reliable manufacturers, such as those endorsed by independent organizations like National Science Foundation (NSF) International.

Index Terms - Nutraceuticals, Cardiovascular Disease, Coronary Artery Disease, Stroke, Peripheral Artery Disease, Medicinal Plants

Introduction: The term "nutraceutical" is derived from the combination of "nutrient," referring to nourishing food components, and "pharmaceutical," denoting medical drugs. Introduced in 1989 by Stephen DeFelice, the creator and leader of the Foundation for Innovation in Medicine, located in Cranford, New Jersey, nutraceuticals embody the preventive philosophy inspired by the ancient Greek physician Hippocrates, often quoted as saying, "let food be your medicine." Investigating their role in human nutrition reveals profound implications for consumers, healthcare providers, regulators, food producers, and distributors [1,2].

In recent years, nutraceuticals have garnered significant attention due to their potential nutritional, safety, and therapeutic benefits. These products play a role in diverse biological processes, encompassing antioxidant defenses, cell proliferation, gene expression, and the preservation of mitochondrial integrity. As a result, nutraceuticals can be utilized to improve health, mitigate chronic diseases, and slow down the aging process, and thereby increase life expectancy, or simply support the overall functions and integrity of the body. Recognized as valuable sources for preventing life-threatening conditions such as diabetes, renal and gastrointestinal disorders, as well as various infections, these products are considered conducive to a healthy lifestyle [3,4].

1. Cardiovascular Disease (CVD): CVD encompasses a spectrum of conditions affecting the heart or blood vessels. This category includes various diseases such as coronary artery diseases (e.g., angina, heart attack), heart failure, hypertensive heart disease, rheumatic heart disease, cardiomyopathy, arrhythmia, congenital heart disease, valvular heart disease, carditis, aortic aneurysms, peripheral artery disease, thromboembolic disease, and venous thrombosis [4,5]

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1.1 TYPES OF CVD

There are four main types of CVD

- Coronary Heart Disease
- Stroke
- Peripheral Arterial Disease
- Aortic Disease

(A). Coronary Heart Disease: Coronary heart disease (CHD) occurs when the flow of blood to the heart muscle is hindered or interrupted due to the buildup of fatty substances (atheroma) in the coronary arteries. These arteries are essential for supplying blood to the heart. In cases where the coronary arteries narrow due to atheroma buildup, the blood flow to the heart muscle may be limited, leading to the onset of angina (chest pains). In more severe instances, if a coronary artery becomes entirely obstructed, it can result in a heart attack, constituting a medical emergency [6].

Cardamom: The essential oil of cardamom has been documented to contain specific bioactive components demonstrating hypocholesterolemic, hypoglycemic, hyperlipidemic, anti-oxidative stress, anti-inflammatory, and antimutagenic properties. It acts by activating antioxidant enzymes, thereby reducing the unfavorable oxidation of LDL-C. Treatment with cardamom oil has resulted in an increased HDL ratio, while significantly lowering levels of triglycerides, total cholesterol, phospholipids, LDL, and very LDL (VLDL) in the serum. Additionally, cardamom extract exhibits anti-atherosclerotic potential, leading to reductions in total cholesterol, triglycerides, and phospholipids within aortic tissues. Furthermore, it demonstrates a protective effect against severe and acute anxiety-induced myocardial injuries, (VLDL) in the serum were significantly lowered [7,8].

(B). Stroke: A stroke is a critical medical condition that occurs when there is a disruption in the blood supply to the brain. Much like all organs, the brain requires a continuous flow of oxygen and nutrients for proper functioning, a supply provided by the bloodstream. If the blood flow is constrained or halted, it results in the death of brain cells, leading to potential brain damage and even death. Given the severity of the situation, a stroke qualifies as a medical emergency, necessitating swift and immediate treatment. The timeliness of intervention plays a crucial role in minimizing potential damage.

The primary symptoms of a stroke are encapsulated in the acronym FAST, representing:

- Face – observable drooping on one side, an inability to smile, or drooping of the mouth or eye
- Arms – difficulty lifting or maintaining the raised position of one arm due to weakness or numbness
- Speech – slurred or garbled speech, or an inability to communicate despite appearing awake

• Time – an urgent need to dial emergency services (999) if any of these signs or symptoms are observed [9,10].

(C) Peripheral Arterial Disease: it alternatively termed peripheral vascular disease arises when there is an obstruction in the arteries that supply blood to the limbs, typically affecting the legs. A prevalent symptom of peripheral arterial disease manifests as pain in the legs during walking commonly experienced in one or both thighs, hips, or calves. The discomfort can be akin to cramping, a persistent ache, or a sensation of heaviness in the leg muscles. Typically, this pain is intermittent, exacerbating during physical activities involving the legs, such as walking or ascending stairs [11]

(D) Aortic Disease: The aorta, the largest blood vessel in the body, plays the crucial role of transporting blood from the heart to all other parts of the body. A prevalent form of aortic disease is the aortic aneurysm, characterized by the weakening of the aorta's wall, causing it to bulge outward. Typically, individuals with this condition commonly report pain in the chest, back, or abdominal region [12].

1.2 Hypertension: Hypertension stands out as a crucial risk factor for cardiovascular diseases (CVDs) and stands as a primary driver of elevated mortality rates in developed nations. The estimated lifelong risk of developing hypertension is approximately 90%, emphasizing the significance of a proactive non-pharmacologic approach to preemptively address potential complications. Additionally, hypertension manifests as an insidious condition, with elusive symptoms that are challenging to detect. Consequently, the progression of organ damage in individuals with hypertension may occur before the pathology is accurately addressed [13].

Nutraceutical used: (i) **Resveratrol:** Resveratrol (3,4,5-trihydroxy-trans-stilbene), often abbreviated as RES, is a potent antioxidant present in significant concentrations in grape skin. Several studies have illustrated the antihypertensive effects of RES in various preclinical hypertensive models. These effects encompass diverse mechanisms, including antioxidant action, stimulation of endothelial nitric oxide (NO) production, inhibition of vascular inflammation, and prevention of platelet aggregation. Notably, besides lowering blood pressure (BP) levels, RES has demonstrated protective effects in animals with dyslipidemias and insulin resistance. It has also displayed the ability to reduce cardiac hypertrophy and contractile dysfunction. The fundamental mechanisms underlying RES's beneficial effects primarily rely on the endothelium-dependent pathway, involving the AMPK, SIRT-1, and Nrf2 pathways, all linked to enhanced NO availability through increased eNOS activity and decreased vascular smooth cell contractility via Ang-II inhibition [14].

(ii) **Cocoa:** The daily consumption of flavonoids, linked to a reduced risk of coronary heart disease, stroke, and general cardiovascular diseases (CVDs), is noteworthy. Various food-derived flavonoids display vascular protective effects by means of their antioxidant and anti-inflammatory properties, promoting nitric oxide (NO) metabolism and endothelial function. Extensive research has been conducted on cocoa, which is abundant in oligomeric procyanidins. Notably, flavonoids found in chocolate enhance NO bioavailability, protect the vascular endothelium, and mitigate CVD risk factors such as insulin resistance and systemic inflammation by increasing plasma antioxidant capacity. Clinical trials have illustrated cocoa's capacity to augment peripheral vasodilation, enhance antioxidant status, and lower blood pressure, ultimately leading to an overall improvement in coronary function in humans [15,16].

(iii) **Curcumin:** it is a yellow/orange plant pigment, has been linked to numerous cardiovascular advantages, such as antioxidative, anti-inflammatory, and anti-proliferative effects, as well as calcium homeostatic properties. These functions contribute to lowering blood pressure levels and preventing vascular smooth cell proliferation. In rat models, curcumin prevented hypertension by reducing AT1R expression in arteries and acetylating GATA [17].

(iv) **Berberine:** it is, a plant alkaloid possessing various properties, demonstrates antihypertensive effects by inducing vasodilation in both endothelial and vascular smooth muscle. The vasodilation in vascular smooth muscle seems to depend on the dosage and is linked to heightened nitric oxide (NO) release (facilitated by increased endothelial nitric oxide synthase or eNOS expression), diminished angiotensin-converting enzyme (ACE) impact, balanced activation of potassium (K⁺) channels, and the release of intracellular calcium ions (Ca⁺⁺). Additionally, Berberine provides long-term protection against

hypertension by inhibiting vascular smooth cell growth and activation induced by platelet-derived growth factor (PDGF), thereby reducing overall proliferation and counteracting structural and functional changes in the vasculature [18].

1.3 Atherosclerosis: it is a degenerative disease with multiple contributing factors that impacts medium to large caliber arteries, causing inflammation and stiffening. This condition results from the accumulation of oxidized lipids and white blood cells in the arterial walls. Typically, atherosclerosis manifests in adulthood or advanced age. The deposits, referred to as atheromas or atherosclerotic plaques, are situated in the innermost layer of the arteries, which directly interacts with the bloodstream. The progression of these lesions is dynamic; initially, they manifest as reversible lipid streaks in childhood and, over several decades, tend to transform into atherosclerotic plaques, particularly in individuals predisposed to the condition and those who neglect risk factor prevention [1,2,3,4,5].

Nutraceuticals Used: (i) Quercetin: it is found abundantly in various sources such as green leafy vegetables, nuts, flowers, barks, broccoli, olive oil, apples, onions, green tea, red grapes, dark cherries, blueberries, and cranberries. Clinical trials involving humans have indicated that quercetin exhibits anti-inflammatory properties by reducing CRP levels, playing a crucial role in preventing atherosclerosis. Furthermore, quercetin has been observed to decrease blood LDL cholesterol levels and inhibit LDL oxidation by macrophages in overweight individuals at high cardiovascular risk. Notably, these effects are associated with quercetin's ability to induce maturation and apoptosis of human fat cells, as well as inhibit blood glucose uptake from fat cells in vitro. The mechanisms underlying its anti-inflammatory, anti-proliferative, and anti-atherosclerotic effects involve the activation of SIRT1, which modulates the AMPK/NADPH oxidase/AKT/endothelial NO synthase signaling pathway. Additionally, these effects are attributed to the suppression of ox-LDL-induced endothelial oxidative stress. In Apo E knockout mice subjected to a high-fat diet (HFD) to simulate atherosclerosis, quercetin demonstrated the suppression of ROS-induced ox-LDL production and inhibition of p47phox levels [5,6].

(ii) Berberine: Conflicting findings exist regarding the impact of berberine on atherosclerosis. While it reduces serum cholesterol levels in humans and hamsters by inducing LDL receptors in hepatic cells, it also stimulates foam cell formation in apoE^{-/-} mice, RAW264.7 mouse cells, and human primary macrophages by inducing scavenger receptor A (SR-A) expression and modified LDL uptake. This dual effect complicates the assessment of berberine's overall effects. Nevertheless, clinical research indicates a protective effect on atherosclerosis in humans. A single-blind clinical study involving 40 moderate dyslipidemic subjects treated with a berberine combination with other nutraceuticals for 4 weeks demonstrated a significant reduction in total cholesterol by 16–20%, LDL-c by 20–25%, ApoB by 15–29%, and triglycerides by 22–26%, with a simultaneous increase in LDL-c by 5.1–6.6% [6,7].

(iii) Spirulina Platensis: Spirulina extracts have been utilized to address dyslipidemia. Several studies have emphasized the impact of peptides isolated from the gastric enzymatic hydrolysate of Spirulina on early atherosclerotic responses induced by histamine in EA.hy926 endothelial cells. Specifically, two tetrapeptides, Leu-Asp-Ala-Val-Gln-Arg and Met-Met-Leu-Asp-Phe, were identified for their ability to inhibit the production of adhesion molecules, such as P-selectin and E-selectin, leading to a reduction in in vitro monocyte adhesion onto endothelial cells. Furthermore, Spirulina extracts have exhibited the capacity to decrease total cholesterol, triglyceride, and LDL-C levels while improving HDL-C levels in diet-induced hypercholesterolemic rabbits and mice, as well as in human trials [19].

1.4 Dyslipidemia: it encompasses various lipid abnormalities that elevate the susceptibility to cardiovascular disease (CVD). Lowering total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) proves effective in both primary and secondary prevention of CVD events. Notably, maintaining low levels of LDL-C is correlated with decreased incidence of major coronary events [20].

Nutraceuticals Used: (i) Sterols/stanols: The intake of plant sterols/stanols has been shown to associate with decreased levels of total cholesterol (TC) in humans. The main effect is observed in the reduction of LDL cholesterol (LDL-C), with little to no impact on high-density lipoprotein cholesterol (HDL-C) or triglycerides. The mechanism by which sterols/stanols lower LDL-C includes a decrease in the absorption of cholesterol in the intestines, the enhancement of hepatic LDL receptors (leading to increased uptake of hepatic cholesterol), and a decrease in the production of endogenous cholesterol [21].

(ii) Polyphenols: Various research studies have indicated that grape polyphenols can influence plasma lipid levels. The consumption of grape juice has been associated with an increase in HDL-C. An exploration of the influence of a polyphenol-rich grape extract supplement (700 mg) on cardiovascular risk in healthy individuals demonstrated a decrease in plasma TC and LDL-C concentration. However, a more comprehensive meta-analysis, involving nine randomized controlled trials with a total of 390 participants, did not reveal a significant effect of grape seed extract on LDL-C. Although no overall impact was observed in this combined population, more targeted examinations of subpopulations and advanced lipid analyses have been undertaken in other investigations. For instance, one study observed a reduction in plasma concentrations of large LDL-C and large LDL particles in obese subjects who were supplemented with grape powder for 3 weeks, although the atherogenic small LDL particles remained unaffected by the treatment [4,5].

(iii) Spirulina: Supplementation with Spirulina has been correlated with favorable changes in blood lipid profiles. Administration of Spirulina maxima orally (4.5 g/day for 6 weeks) demonstrated significant alterations in concentrations of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C). Additionally, in individuals with dyslipidemia, the daily intake of 1 g Spirulina for 12 weeks led to reduced mean levels of triglycerides, LDL-C, and TC, without observable effects on high-density lipoprotein cholesterol (HDL-C). A recent meta-analysis of seven randomized controlled trials examining Spirulina seemed to support these findings. Nonetheless, further well-designed trials are necessary to clarify the mechanism of action of Spirulina supplementation in dyslipidemia and ascertain its effects on cardiovascular outcomes [21].

Conclusion: In summary, the nutraceuticals industry has the potential to grow and involves both nutrition and medical treatment to provide comprehensive medical support. They may be used as nutritional supplements, to cure and prevent different forms of cancer, to prevent disorders including cardiovascular disease, and for other medical purposes. As a result, the nutraceutical companies have a thorough understanding of the possible benefits of nutrients for human health. Currently, it is believed that medications belong in the medical field. Conversely, nutrition is only considered a product for leading a healthy lifestyle. As they both interact and complement one another, work is expected to be done in the upcoming years. Better medical treatment and health care benefits are brought about by the application of modern technologies, such as genetically modified food in the food sector and nutraceuticals based on nanotechnology. This has further expanded the growth of the nutraceuticals revenue market. Scientific research confirms that the enhanced safety and potential benefits of recently created nutraceutical products will encourage investments in more advanced technologies, including nutrigenomics, convergent approaches, diverse imaging technologies, and their uses in the development of nutrition and healthcare.

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