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ROLE OF NUTRACEUTICALS AND DIET IN PREVENTING CARDIOVASCULAR DISEASES

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ABSTRACT

Cardiovascular disease (CVD) is one of the most frequent health-related and economic challenges globally. Dietary variables significantly contribute to cardiovascular risk, either directly or indirectly through their influence on other cardiovascular risk factors such as hypertension, dyslipidemia, and diabetes mellitus. Nutraceuticals are natural nutritional substances that have been found to be effective in both preventive and therapeutic applications. Several foods and dietary supplements have been demonstrated to help prevent the development of CVD. The purpose of this review is to provide an update on the most recent data on the use of nutraceuticals in the prevention and treatment of CVD.

KEYWORDS: Nutraceuticals, cardiovascular disease (CVD), and polyphenols.

INTRODUCTION

Cardiovascular disease (CVD) is widespread, with the majority of persons over the age of sixty experiencing some kind of CVD. Based on statistics from 2012 and 2013, CVD is expected to cause 17.3 million deaths worldwide each year.[1] Morbidity is also significant, and CVD accounts for 200 billion Euros in European healthcare cost.[2] There are two types of CVD risk factors: modifiable and non- modifiable. Obesity, hypertension, hyperlipidemia, diabetes mellitus, metabolic syndrome, and bad diet, smoking, and physical inactivity are all modifiable risk factors. Dietary variables also contribute significantly to cardiovascular risk, either directly or through their influence on other risk factors such as hypertension, dyslipidemia, and diabetes mellitus.[3] Protective effects against cardiovascular disease (CVD) have been evidenced for a variety of foods and dietary supplements,[5] thus offering new potential for reducing CVD risk at the population level. Evidence indicates that this approach is highly promising. For instance, in the PREDIMED observational study, those in the highest quintile of polyphenol consumption had a relative CVD risk that was 54% lower than those in the lowest quintile.[6] This review aims to present an update on the most recent findings related to the use of nutraceuticals in the prevention and treatment of CVD. Unfortunately, there are few studies that have evaluated the associations between nutraceutical consumption and significant outcomes such as mortality. Large randomized controlled trials are particularly infrequent, resulting in a lack of evidence in this area. Thus, our discussion will primarily focus on the effects of nutraceuticals on well-characterized CVD risk factors.

CVD

Cardiovascular diseases are a group of disorders that affect the heart and blood vessels. They are the leading cause of death globally, accounting for approximately 17.9 million deaths per year.

Types of Cardiovascular Diseases

- Coronary Artery Disease: Occurs when the blood vessels supplying the heart become narrowed or blocked.
- Heart Failure: When the heart can't pump enough blood to meet the body's needs.
- Arrhythmias: Irregular heartbeats that can be too fast, too slow, or erratic.
- Stroke: When the blood supply to the brain is interrupted or reduced.
- Peripheral Artery Disease: Narrowed arteries reducing blood flow to the limbs.

Causes and Risk Factors

- High Blood Pressure: A major risk factor for cardiovascular diseases.
- High Cholesterol: A major risk factor for cardiovascular diseases.
- Smoking: A major risk factor for cardiovascular

diseases.
- Diabetes: A major risk factor for cardiovascular diseases.
- Obesity: A major risk factor for cardiovascular diseases.

Symptoms
1. Chest Pain: A common symptom of coronary artery disease.
2. Shortness of Breath: A common symptom of heart failure.
3. Fatigue: A common symptom of heart failure.
4. Dizziness: A common symptom of arrhythmias.
5. Pain or Numbness: A common symptom of peripheral artery disease.

Prevention and Treatment
1. Healthy Diet: Eating a balanced diet rich in fruits, vegetables, and whole grains.
2. Regular Exercise: Exercising regularly to maintain a healthy weight and reduce risk factors.
3. Not Smoking: Quitting smoking to reduce risk factors.
4. Medications: Taking medications to manage blood pressure, cholesterol, and diabetes.
5. Surgery: Undergoing surgery to treat severe cardiovascular diseases.

Nutraceuticals

The phrase "nutraceuticals" was coined by Stephen DeFelice, the founder and chairman of the Foundation for Innovation in Medicine, in 1989. A nutraceutical is defined as a "food, or parts of a food, that confer medical or health benefits, including the prevention and treatment of disease".[7] This definition includes medicinal products derived from natural sources. Several categories of nutraceuticals have been suggested to have potential benefits in the management of cardiovascular disease (CVD), with those supported by the strongest evidence summarized below.

Sterols/stanols

Plant sterols and stanols are types of phytosterols, identified in a variety of plant products such as different fruits and vegetables, cereals, seeds, and nuts. Their biological activity is due to their structural similarity to cholesterol.[8]

Polyphenols

Polyphenols are phytochemicals that are widely distributed in foods of plant origin. They can be found in fruits, vegetables, cereals, and legumes. Additionally, they are present in beverages made from plant products such as tea, coffee, wine, and cocoa. Polyphenols are structurally diverse, with over 8,000 identified types. These include flavonoids, phenolic acids, stilbenes, and lignans.[9] Polyphenols found in grapes and grape derivatives, cocoa, and tea are particularly relevant for CVD prevention. Phenolic compounds found in grapes include anthocyanins, flavanols, flavonols, stilbenes, and phenolic acids.[10] Resveratrol (3,5,4'-trihydroxy- trans-stilbene) is the most extensively studied stilbene derived from grapes, primarily found in grapes. However, resveratrol is also present in various other species, including cranberries, blueberries, peanuts, and Japanese knotweed.[11] Cocoa bean derivatives (Theobroma cacao) are commonly consumed in cocoa and chocolate.[12] A variety of polyphenols have been identified in cocoa and its derivatives, including catechins, flavonol glycosides, anthocyanins, and procyanidins.[13] Foods that contain cocoa provide a higher concentration of flavonoids, which are beneficial.

The widespread and frequent consumption of tea necessitates an investigation into its essential nutraceutical properties. Tea contains polyphenols such as catechins, theaflavins, tannins, and flavonoids. The chemical composition is influenced by the degree of fermentation of the tea leaves. Green tea, which undergoes minimal fermentation, is rich in catechins like epigallocatechin gallate, epicatechin-3- gallate, epigallocatechin, and epicatechin,[15] while black tea, which is more extensively fermented, is abundant in flavins and thearubigins.[16]

Spirulina

Spirulina is a blue-green microalga (Cyanobacterium) that serves as a rich source of protein, vitamins, minerals, carotenoids, and phycocyanins. It has a long history of use as a human food source with no significant safety concerns.[17,18] Table S1 provides a summary of the methodology and key findings from each study discussed in the paper.

Dyslipidemia

Dyslipidemia refers to a range of lipid abnormalities that elevate the risk of cardiovascular disease (CVD). Lowering total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) is effective for both primary and secondary prevention of CVD events.[76] Notably, lower LDL-C levels correlate with reduced rates of major coronary events.[77] Therefore, nutraceuticals that can alter the plasma lipid profile may help alleviate the burden of CVD.[78] Evidence regarding the lipid-modifying effects of nutraceuticals is summarized below.

Sterols/stanols: The intake of plant sterols and stanols has been linked to reduced circulating levels of TC in humans.[79,80] Their primary effect is the reduction of LDL-C, with minimal or no impact on high-density lipoprotein cholesterol (HDL-C) or triglycerides.[81] The mechanism through which sterols and stanols lower LDL-C involves decreased intestinal absorption of cholesterol, increased hepatic LDL receptor activity (leading to enhanced hepatic cholesterol uptake), and reduced endogenous cholesterol production.[82] Circulating levels of LDL-C are negatively correlated with the amount of sterol/stanol intake. The decrease in plasma LDL-C levels linked to sterol/stanol consumption can be as significant as 10%.[19,20] This reduction may

contribute to lower cardiovascular disease (CVD) rates if it correlates with a decrease in cardiovascular events, similar to the effects of other lipid-lowering medications. Since sterols/stanols diminish the intestinal absorption of cholesterol, their impact may complement that of statins, which work by decreasing hepatic cholesterol production. Notably, a meta-analysis of 15 randomized controlled trials suggests this synergy. It was observed that combining statins with stanols/sterols resulted in a more significant reduction in total cholesterol (TC) and LDL-C levels compared to using statins alone. The addition of sterols/stanols did not affect HDL-C and triglyceride levels when used alongside statin therapy.[21] Another meta- analysis indicated that the lipid-lowering effectiveness of plant sterols/stanols was comparable whether they were consumed through diet or taken as a nutraceutical supplement,[19] providing flexibility in delivery methods. There is some evidence regarding the impact of sterol intake on cardiovascular outcomes. Observational studies imply that a high consumption of plant sterols may be linked to the prevention of myocardial infarction (MI) in men.[22] A recent large observational study found that natural phytosterol intake was associated with reductions in TC and LDL- C, particularly among men. However, this positive effect on lipid profiles did not lead to a decreased risk of CVD.[23] One possible reason for the lack of correlation between LDL-C reduction and CVD risk is that sterols/stanols might inhibit the absorption of carotenoids and fat-soluble vitamins.[83] Such an effect could potentially lead to a higher incidence of CVD,[84] but further research is necessary to confirm whether this occurs in vivo.

- Nutraceuticals play a significant role in the prevention of cardiovascular diseases. These natural substances, which include flavonoids, phytosterols, omega-3 fatty acids, green tea, turmeric, and ginger, have been shown to have a positive impact on cardiovascular health.

Role of Flavonoids

Flavonoids, found in veggies, onions, grapefruits, and apples, block the angiotensin-converting enzyme (ACE) that raises blood pressure. This can help to reduce the risk of heart disease and stroke because high blood pressure is a major risk factor for these conditions.

Role of Phytosterols

Phytosterols, which are plant sterols, compete with dietary cholesterol, blocking its uptake and facilitating its excretion from the body. This can help to lower cholesterol levels and reduce the risk of heart disease because high cholesterol is a major risk factor for heart disease.

Role of Omega-3 Fatty Acids

Omega-3 fatty acids, found in fish, have anti-arrhythmic, hypolipidemic, and antithrombotic effects. This means that they can help to regulate heartbeat, lower triglycerides, and prevent blood clots. These effects can help to reduce the risk of heart disease because irregular heartbeat, high triglycerides, and blood clots are all major risk factors for heart disease.

Role of Green Tea

Green tea contains antioxidants like epigallocatechin that can lower cholesterol and blood pressure. This can help to reduce the risk of heart disease because high cholesterol and blood pressure are major risk factors for heart disease.

Role of Turmeric

Turmeric, which contains curcumin, improves endothelial function and decreases heart attack risk by 65 percent. This is because curcumin has anti- inflammatory and antioxidant effects that can help to improve blood vessel function and reduce the risk of heart disease.

Role of Ginger

Ginger, which contains gingerol, has anti- inflammatory effects. This can help to reduce the risk of heart disease because inflammation is a major risk factor for heart disease.

Benefits of Nutraceuticals

The benefits of nutraceuticals in preventing cardiovascular diseases are numerous. They can help to:

- Reduce inflammation
- Improve heart health
- Lower blood pressure
- Reduce the risk of heart disease
- Prevent the buildup of plaque in arteries
- Reduce the risk of heart attack and stroke

The Protective Role of Diet in Cardiovascular Disease

It has been suggested that lifestyle modifications, particularly dietary changes, can help prevent cardiovascular disease (CVD).[8] Initial evidence regarding the impact of diet on CVD emerged from analyses of food consumption trends, and ecological studies have indicated links between the prevalence of CVD and fat consumption.[3] Furthermore, the overconsumption of calorie-dense, nutritionally deficient, highly processed foods that are quickly absorbed can result in systemic inflammation, decreased insulin sensitivity, and a range of metabolic issues, such as obesity, hypertension, dyslipidemia, and glucose intolerance.[9] Recently, nutrition research has increasingly focused on understanding the effects of whole foods.[10] A comprehensive strategy that integrates lifestyle changes with appropriate pharmacological treatments is being pursued to lower cardiovascular risk factors, enhance vascular health, and decrease healthcare costs.[11] While epidemiological research has established a connection between diet and CVD, significant scientific uncertainty remains regarding the specific dietary components and their impact on cardiovascular risk. Observational and prospective cohort studies

indicate that a higher intake of dietary antioxidants or their supplementation correlates with a reduced risk of CVD and mortality; however, clinical trial evidence remains predominantly negative.[12] The contradictory findings between the seemingly protective effects of nutrients within dietary intake and the ineffectiveness of single nutrient supplementation in trials have shifted the focus towards whole foods or modified diets as protective measures against CVD.[13] Oxidative stress can be defined as an imbalance in the pro-oxidant/antioxidant equilibrium that promotes oxidation. It has been proposed that oxidative stress plays a role in the development of various chronic diseases, including CVD, diabetes, stroke, certain cancers, and neurodegenerative conditions.[14] Dietary nutrients, both water-soluble and lipid-soluble, represent a crucial element of the antioxidant defense system.

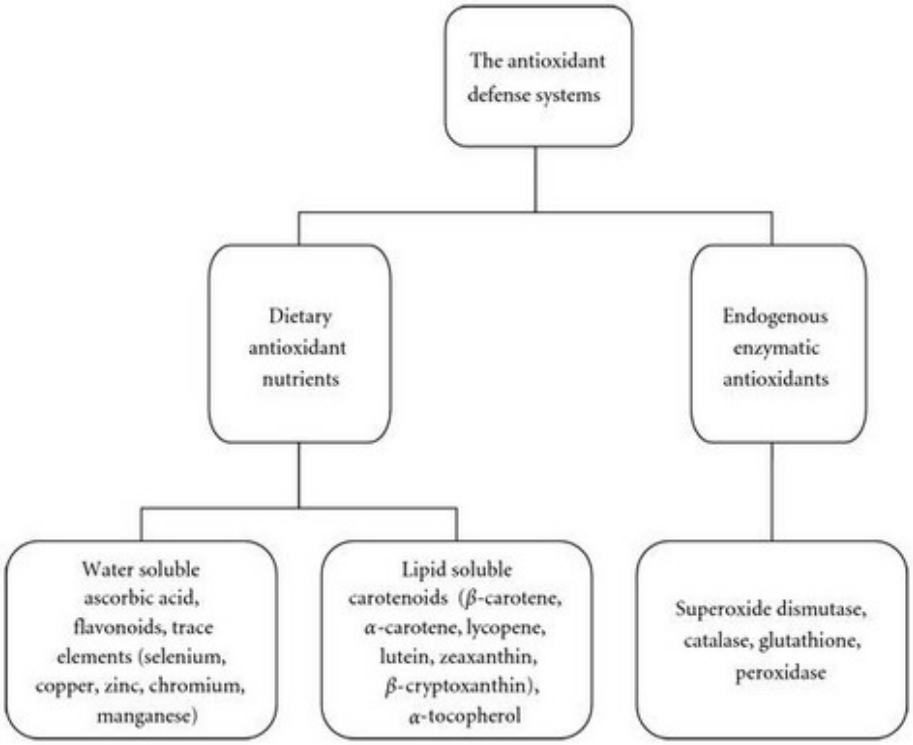

Figure 1: The antioxidant defence system.

The antioxidant defense system comprise, endogenous enzymatic and exogenous nonenzymatic nutrients. The dietary antioxidant nutrients can either be water soluble or lipid soluble. There are also other dietary constituents that may have either direct antioxidant activity or indirect antioxidant activity such as trace elements that are constituents of antioxidant enzymes.

- In addition to their typical presence in the cells and tissues of living organisms, free radicals and reactive species are also generated in the foods that individuals consume daily, leading to unwanted reactions such as the oxidation of lipids, proteins, nucleic acids, and carbohydrates. A reduced ability to neutralize free radicals and reactive species, often due to diminished levels of antioxidant cellular defense systems or an overproduction of free radicals, is frequently observed in critical organs such as the brain, liver, and heart in both humans and animals.[15,16] Initially, it was believed that antioxidant vitamins would provide a straightforward method to mitigate the heightened oxidative stress caused by cardiovascular risk factors. However, it was discovered that high doses of certain antioxidant vitamins could have negative effects on vascular health. The impact of antioxidant supplements on overall mortality in adults participating in primary and secondary prevention trials, particularly those treated with beta carotene, vitamin A, and vitamin E, may actually lead to increased mortality, and further investigation is required regarding the potential influence of vitamin C and selenium on mortality.[17,18]

Role of Diet in prevention of CVD'S

Diet plays a crucial role in the prevention of cardiovascular diseases. A well-balanced diet that is rich in nutrients and antioxidants can help to reduce the risk of heart disease. Here's a breakdown of the role of diet in preventing cardiovascular diseases:

Key Dietary Recommendations

1. Fruits and Vegetables: Rich in antioxidants, vitamins, and minerals. Leafy greens like spinach and kale, berries like blueberries and strawberries, and citrus fruits like oranges and grapefruits are all excellent choices.
2. Whole Grains: Rich in dietary fiber and phytosterols. Brown rice, quinoa, and whole wheat

bread are all good options.
3. Lean Proteins: Rich in omega-3 fatty acids. Fatty fish like salmon and sardines, lean meats like chicken and turkey, and legumes like lentils and chickpeas are all excellent choices.
4. Healthy Fats: Rich in antioxidants and omega-3 fatty acids. Nuts and seeds like almonds and chia seeds are all good options.

Benefits of a Balanced Diet
1. Reduces Inflammation: A balanced diet can help to reduce inflammation, which is a major risk factor for heart disease.
2. Improves Heart Health: A balanced diet can help to improve heart health by reducing the risk of heart disease.
3. Lowers Blood Pressure: A balanced diet can help to lower blood pressure, which is a major risk factor for heart disease.
4. Reduces the Risk of Heart Disease: A balanced diet can help to reduce the risk of heart disease by providing the body with the nutrients it needs to function properly.

Nutraceuticals in the Diet: Nutraceuticals like flavonoids, phytosterols, omega-3 fatty acids, green tea, turmeric, and ginger can be incorporated into the diet to help prevent cardiovascular diseases. These substances have been shown to have a positive impact on cardiovascular health.

Bioactive Dietary Compounds with Cardioprotective Properties

Early studies assessed the advantages of plant-based foods by examining their vitamin C, vitamin E, and carotenoid levels.[24] More recent investigations have highlighted the correlation of benefits with specific compounds. Nevertheless, the effects observed when testing these compounds in isolation may be attributed to the synergistic interactions of numerous other bioactive substances found in the source materials.[98] The primary question regarding their effectiveness—whether they should be consumed as part of a whole food diet or taken as supplements—remains unresolved and will be addressed in the following discussion. Each category of bioactive compounds typically includes several members, as will be elaborated upon next.

- Phytochemicals Plant-based foods are rich in bioactive substances referred to as "phytochemicals." Notable groups of phytochemicals that exhibit or seem to exhibit significant health benefits include carotenoids, phenolic compounds (such as flavonoids, phytoestrogens, and phenolic acids), phytosterols and phytostanols, tocotrienols, organosulfur compounds, and nondigestible carbohydrates (including dietary fiber and prebiotics). Isoflavones are particularly abundant in soybeans, soy products (like tofu), and red clover. Lignans are predominantly found in flaxseed.

- Polyphenol Compounds In vivo studies have demonstrated that polyphenols can have antiatherosclerotic effects during the initial stages of atherosclerosis development (for instance, by reducing LDL oxidation); enhancing endothelial function and promoting nitric oxide release (a powerful vasodilator); modulating inflammation and lipid metabolism (i.e., exhibiting a hypolipidemic effect); improving antioxidant status; and providing protection against atherothrombotic events, including myocardial ischemia and platelet aggregation (Perez- Jimenez and Saura-Calixto, 2008).[99]

- Flavonoids: Flavonoids derived from plants represent the most prevalent category of polyphenols in the human diet, found in vegetables and fruits, as well as in beverages like cocoa, tea, and wine. Certain isoflavones, such as lignans, function as phytoestrogens.

- Vitamin E: In addition to functioning as a free radical scavenger, vitamin E serves as a powerful anti-inflammatory agent, particularly at elevated doses. Increasing evidence indicates a strong inverse relationship between plasma vitamin E levels and cardiovascular disease (CVD), as well as between vitamin E consumption and the risk of coronary heart disease (CHD). However, clinical trials have not substantiated the effectiveness of vitamin E supplementation in preventing CVD. Following this, meta- analyses and systematic reviews encompassing over 90 trials have yielded similar negative findings. Most recently, a dose-response meta-analysis indicated an increased risk of total mortality associated with high-dose vitamin E (≥400 IU/day).[17] Several potential reasons exist for these predominantly negative outcomes, including the choice of the most suitable form and/or dosage of vitamin E. This may be crucial for achieving a significant reduction in oxidative stress. Similar to carotenoids, the disparity between results from observational and interventional studies implies that the protective benefits of α-tocopherol are most pronounced when accompanied by other nutrients, making it safest and most effective when sourced from food sources.

Functional Foods with Health- Related Properties

The contradictory findings regarding the protective benefits of nutrients within whole food consumption versus the ineffectiveness of isolated nutrient supplementation in studies have shifted attention towards whole foods as a defense against cardiovascular disease (CVD). Populations that consume a significant amount of plant-based foods, such as fruits and vegetables, or those with a high seafood intake, are recognized to have a reduced occurrence of CVD and specific cancer types.[24] These observations have sparked considerable interest among manufacturers, consumers, and health

professionals in functional foods and nutraceuticals.

Functional foods, which include physiologically active ingredients derived from either plant or animal sources, are promoted with claims of their potential to lower heart disease risk by primarily addressing established risk factors, including blood cholesterol, diabetes, and hypertension. It is believed that functional foods may provide cardioprotective benefits mainly through their ability to lower lipid levels, exhibit antioxidant properties, and/or reduce homocysteine concentrations.

CONCLUSION

The connection between dietary elements and cardiovascular disease (CVD) has been a significant area of health research for nearly fifty years. Both epidemiological and clinical studies suggest that a diet abundant in fruits, vegetables, unrefined grains, fish, and low-fat dairy products, while low in saturated fats and sodium, can decrease the risk of CVD.[11] Additionally, foods such as mono- and polyunsaturated fats, brans, nuts, plant sterols, and soy proteins have demonstrated a positive impact on lipid profiles and blood pressure.[9] Innovative dietary strategies for cardiovascular prevention hold considerable importance in both clinical research and practice. Nevertheless, nutrition is an intricate field of study, and it remains uncertain whether a single dietary component or a combination of nutrients and eating habits contributes to any cardioprotective effects. The progress in understanding both the mechanisms of the disease and the components of a healthy diet has opened new pathways for developing dietary strategies aimed at preventing and/or treating CVD. Current scientific evidence indicates that functional foods exert extensive physiological effects in vivo, which can mitigate inflammatory responses and vascular reactivity. These effects are comparable to those of pharmaceutical treatments, yet they are generally safer. While many functional foods have shown significant therapeutic potential, future research should focus on well-structured clinical trials that evaluate various combinations of these nutrients to uncover possible additive and/or synergistic health benefits. Numerous functional foods possess antioxidant and anti-inflammatory properties, although the mechanisms behind these effects may require further exploration. Consequently, incorporating these functional foods into a balanced diet can yield cardiovascular advantages and reduce the risk of cardiovascular diseases.

- Recent findings regarding the potential influence of antioxidant vitamins on atherosclerotic progression suggest that the role of micronutrients is intricate and unlikely to be attributed to a single factor.

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