

Cardiovascular Diseases and Nutraceuticals

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Cardiovascular diseases (CVDs) such as hypertension, atherosclerosis, myocardial infarction, and diabetes are a significant public health problem worldwide. Although several novel pharmacological treatments to reduce the progression of CVDs have been discovered during the last 20 years, the better way to contain the onset of CVDs remains prevention. In this regard, nutraceuticals seem to own a great potential in maintaining human health, exerting important protective cardiovascular effects. In the last years, there has been increased focus on identifying natural compounds with cardiovascular health-promoting effects and also to characterize the molecular mechanisms involved.

Keywords: Cardiovascular Diseases ; nutraceuticals ; hypertension

1. Introduction

Cardiovascular diseases (CVDs) represent the leading cause of death globally ^{[1][2][3]}. It is well known that the common cardiovascular risk factors such as advanced age, hypertension, diabetes, hypercholesterolaemia, left ventricular hypertrophy, and heart failure are the main contributors of cardiovascular complications ^{[4][5][6][7][8][9]}. Unfortunately, the current pharmacological therapies used for the management of CVDs often failed to be effective in patients who are reluctant to undergo multiple-drug regimens, so adherence to therapy is reduced. Thus, an integrative approach capable of improving cardiovascular protection is urgently needed.

In the last decade, the food industry has focused on the characterization and identification of bioactive molecules contained in foods or in natural matrices, which, besides their nutritional value, can bring health benefits, especially in the treatment of chronic diseases. This process started mainly because these natural compounds are characterized by fewer side effects in comparison with pharmacological therapies, so consumers tend to prefer their use for health promotion. Based on these considerations, the last ten years saw the rapid expansion and commercialization of a new class of products, which are based on an enriched or concentrated mixture of bioactive compounds of natural origin, with several healthy claims that are experimentally verified, these are the so-called “nutraceuticals”. These products derive from the term “Nutraceutics” coined by Dr. De Felice in 1989, and they refer to a group of products that fall in the gap between nutrition and pharmacological therapy. Nutraceuticals (from the terms “nutrition” and pharmaceuticals”) are defined as foods or part of foods that share health-promoting effects (“pharmaceutic properties”) and include polyphenols, carotenoids, polyunsaturated fatty acids, and natural peptides. Compared to therapeutics, nutraceuticals do not have patent protection and governmental sanction and may be used either as preventive agents or as adjuvants of traditional therapy. Although the definition of nutraceuticals in part overlaps that of functional foods and the two terms are often considered synonymous, functional foods may be defined as all foods fortified with compounds aimed to enhance nutritional or healthy potential and are not sold in dosage forms, whereas nutraceuticals exists also in form of tablets, capsules, or powder ^{[10][11]}. This marks also the line with respect to dietary supplements, which are usually products that aim to integrate the diet with macro or micronutrients such as amino acids, minerals, and vitamins. In this regard, several natural products represent also a source of vitamins and trace elements. However, many clinical trials failed to show preventive or therapeutic beneficial effects of vitamins in CVDs ^{[12][13]}.

The importance of nutrition in regulating blood pressure is well documented ^{[9][14][15][16][17][18]}. Beyond the reduction in blood pressure values shown for the “Mediterranean diet” and the “DASH Diet”, in recent years, several studies have documented the antihypertensive action of numerous well-known phytochemicals, which are highly present in nutraceutical formulations, such as cocoa flavonoids, which have been demonstrated to reduce systolic and diastolic blood pressure by about 4–5 mmHg and 2–3 mmHg, respectively).

Taking into consideration the potential efficacy, despite the incompleteness of the scientific information available for many nutraceutical active ingredients, in the last few years, the scientific community has gathered a considerable interest in the characterization and validation of natural compounds in CVDs by investigating their molecular mechanisms and initiating numerous clinical trials.

2. Nutraceuticals in Cardiovascular Diseases

We have focused our attention on the possible effects of some interesting nutraceuticals in different CVDs, highlighting their mechanisms of action and their potential in cardiovascular prevention. Although large and numerous clinical trials in humans are missing, with particular regard to some vascular diseases, the beneficial effects of these natural compounds have no shadow of doubt. The beneficial effects of resveratrol have been extensively described in several murine models, demonstrating its ability to reduce BP level, the progression of atherosclerosis, the regulation of glucose metabolism, and its effect on exercise tolerance and fatigue associated with HF in humans. Our review also summarizes the important effects of cocoa extracts on vascular function, highlighting its effects on endothelial vasorelaxation, on the reduction of cholesterol level, and on the activation of GLUT-2 transporters with enhanced insulin receptors phosphorylation in diabetes. On the other hand, quercetin, curcumin, and berberine exert their effects mainly through the activation of the antioxidant defense in all vascular diseases, and they help to protect from all major CVDs. Brassica vegetables, which include different kinds of cabbage, broccoli, cauliflower, Brussels sprouts, and kale, have recently received considerable attention due to their important effect on vascular protection, showing ACE inhibition and renin inhibition, along with the ability to modulate lipid profile, thus demonstrating significant protective effects on the vasculature. At last, but not least, *Spirulina platensis* appears to be the novel frontier of nutraceuticals, since it possesses several beneficial vascular properties, regulating NO release and vascular function and exerting an important effect in hypertensive murine models. Although the protective and therapeutic properties of resveratrol, cocoa, curcumin, and berberine are now well established through clinical trials, further studies are needed to characterize the efficacy and function of brassica and *Spirulina platensis* in humans. It should be also interesting to assess whether a combination of these nutraceuticals could be more efficacious than the single administration alone.

In addition, taking into account the summary of the shared molecular targets ([Figure 1](#)), it should be interesting to evaluate in the future their possible interaction or potentiation. Moreover, it should be better to define which type of subject should be eligible for nutraceutical intervention. The studies here suggest that individuals at high risk to develop CVDs, rather than those with overt signs, may gain more benefits from nutraceutical interventions. For example, this class of subjects may include individuals with borderline values of blood pressure, as well as glucose or triglyceride levels. Another interesting future direction is to characterize how the physiological response to nutraceuticals differs among individuals. To date, while all the listed nutraceuticals have several claimed properties to reduce or positively modulate the wide landscape of cardiovascular events, there is still a lack of knowledge of the molecular mechanism activated by this class of compounds. In this regard, the current and future direction of research is focused on the elucidation of the molecular pathway modulated by these molecules; in this context the employment of metabolomics, which can take the snapshot of a living system following a physiopathological perturbation, is one of the methods of choice. Metabolomics applied to nutraceuticals (Nutrametabolomics) will be the direction to understand in detail the complex link between the regular intake of phytochemicals and the healthy effect observed in several *in vivo* models. The future directions of nutraceuticals must take into consideration all the above-mentioned issues. In addition, another important question to be resolved with regard to nutraceuticals is their bioavailability and tissue accumulation after intake. Although for some of them, such as RSV, the available pharmacokinetic data show poor plasma bioavailability and fast metabolism after oral dose, while curcumin is instead detected in plasma in the form of glucuronide and sulfate conjugates in plasma, we have only few information regarding the absorption and the bioavailability of bioactive products following the intake of quercetin, brassica, cocoa, berberine and *spirulina platensis*.

Figure 1. Schematic summary of the molecular effects of nutraceuticals in different CVDs.

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