

Review Article

Phytochemical Compounds and Protection from Cardiovascular Diseases: A State of the Art

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Cardiovascular diseases represent a worldwide relevant socioeconomical problem. Cardiovascular disease prevention relies also on lifestyle changes, including dietary habits. The cardioprotective effects of several foods and dietary supplements in both animal models and in humans have been explored. It was found that beneficial effects are mainly dependent on antioxidant and anti-inflammatory properties, also involving modulation of mitochondrial function. Resveratrol is one of the most studied phytochemical compounds and it is provided with several benefits in cardiovascular diseases as well as in other pathological conditions (such as cancer). Other relevant compounds are *Brassica oleracea*, curcumin, and berberine, and they all exert beneficial effects in several diseases. In the attempt to provide a comprehensive reference tool for both researchers and clinicians, we summarized in the present paper the existing literature on both preclinical and clinical cardioprotective effects of each mentioned phytochemical. We structured the discussion of each compound by analyzing, first, its cellular molecular targets of action, subsequently focusing on results from applications in both ex vivo and in vivo models, finally discussing the relevance of the compound in the context of human diseases.

1. Introduction

Cardiovascular diseases (CVDs) still remain the primary cause of death worldwide according to the World Health Organization and American Heart Association statistics [1]. Different approaches have been proposed to reduce the high global incidence of CVDs and to improve human health. The consumption of functional foods or dietary supplements for lowering the risk of CVDs has gained attention over the last few years from both scientific and clinical communities [2, 3]. Several antioxidant compounds can be found in vegetables (e.g., vitamins and phenolic compounds). They are partly responsible for the health benefits by scavenging reactive oxygen radicals (ROS) and by inhibiting cellular damage at different levels. Although the literature contains several review articles describing either general health benefits of phytochemical supplements or the cardioprotective effects of

a single phytochemical compound, no comprehensive review article has been so far reported focusing on both preclinical and clinical cardiovascular beneficial effects of the most known compounds (resveratrol, *Brassica oleracea*, curcumin, and berberine).

In the present paper we attempted to fill up this literature gap. In order to reach our goal, we discussed each phytochemical compound by analyzing its molecular targets of action, discussing all existing in vitro, ex vivo, and in vivo data related to its cardiovascular beneficial properties, finally highlighting the evidence available in human CVDs.

2. Resveratrol

Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a natural polyphenolic compound that exists in *Polygonum cuspidatum*, grapes, peanuts, and berries, as well as in their

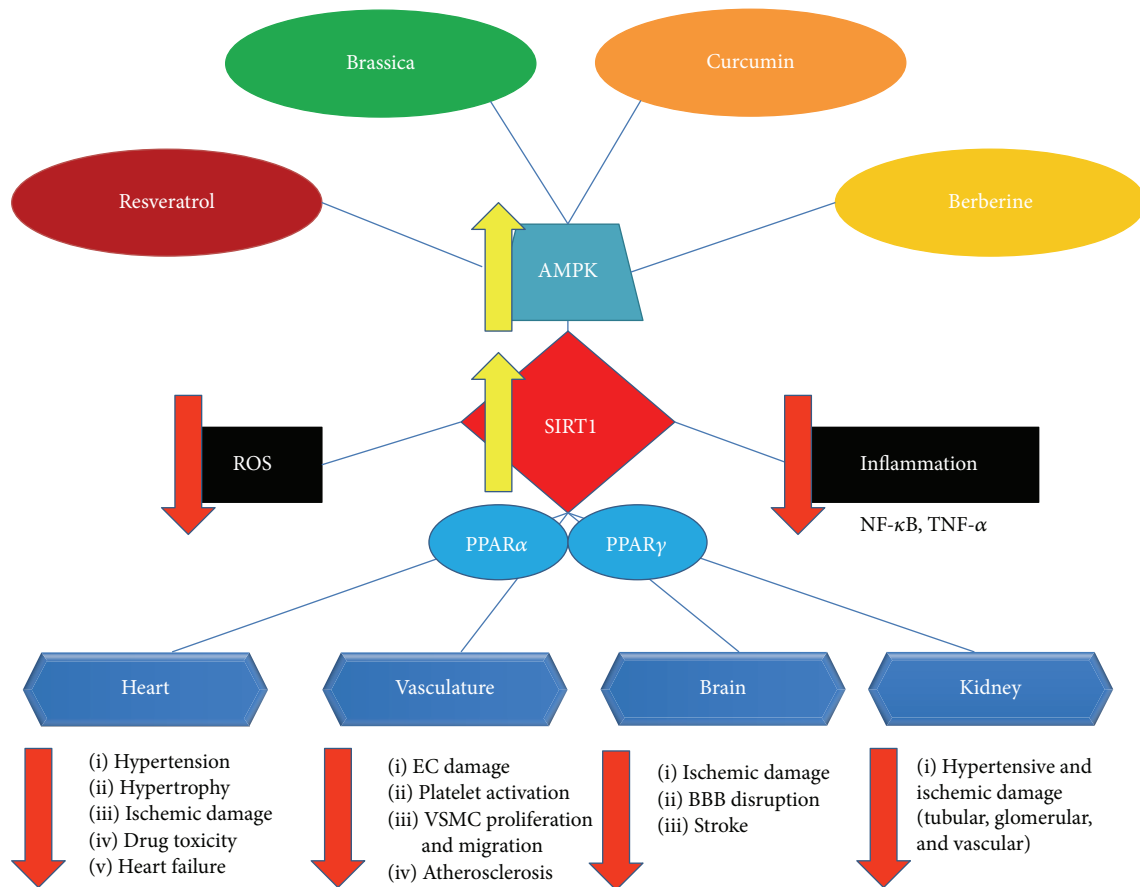


FIGURE 1: Schematic representation of beneficial effects exerted in the cardiovascular system by resveratrol, *Brassica oleracea*, curcumin, and berberine. The AMPK/SIRT-1/PPAR α / γ molecular pathway, underlying most of the effects of all vegetable compounds, is illustrated. AMPK: 5'-adenosine monophosphate-activated protein kinase; SIRT-1: silent mating type information regulation-1; PPAR: peroxisome proliferator-activated receptor; ROS: reactive oxygen species; NF- κ B: nuclear factor- κ B; TNF- α : tumor necrosis factor- α ; EC: endothelial cell; VSMC: vascular smooth muscle cell; BBB: blood brain barrier.

manufactured products, especially red wine [4]. It exists in both *cis*- and *trans*-configurations, of which *trans*-resveratrol is the principal biologically active form [5]. Interestingly, red wine (therefore resveratrol) was supposed to be one of the factors responsible for the “French Paradox,” together with several lifestyle and dietary factors. The term is used to describe the low incidence of CVDs in French population despite its high intake of saturated fats. However, the median daily dose of resveratrol to be protective is estimated to be 20 mg/kg/day, whereas its concentration in red wine is roughly 1.98–7.13 mg/L [6]. Therefore, the assumption of a high quantity of red wine per day would be needed for a man to obtain a protective dose of resveratrol, causing serious health problems [7, 8]. However, an inverse association between moderate alcohol consumption (30–50 gr/day) and CVDs has been assessed in several epidemiological studies. The physiological mechanism of the protective effect of alcohol seems to be at least in part related to its effect in reducing platelet action.

2.1. Molecular Targets and Properties. Resveratrol interacts with multiple targets in cardio- and cerebrovascular

diseases, age-related diseases, cancer, and so forth, [9, 10]. The main molecular mechanism mediating resveratrol biological effects is the 5'-adenosine monophosphate-activated protein kinase (AMPK)/silent mating type information regulation-1 (SIRT-1) pathway (Figure 1) [11, 12]. The precise mechanism through which resveratrol activates SIRT-1 is not completely understood [13]. Other minor pathways mediate some of the resveratrol effects and they will be briefly mentioned below.

The most important properties of resveratrol are connected with oxidative stress, vascular inflammation, and platelet aggregation. In fact, resveratrol upregulates the endogenous antioxidant systems, such as superoxide dismutase (SOD) enzymes, in endothelial cells (ECs) and in cardiac myoblasts and it reduces ROS production [14, 15]. Moreover, it reduces arachidonic acid and prostaglandin E₂ synthesis. It inhibits phospholipase A₂ and cyclooxygenase-2 activity; it antagonizes the function of the most important molecules involved in inflammation, such as nuclear factor- κ B (NF- κ B), tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), inducible nitric oxide synthase (iNOS) activity, and monocyte chemoattractant protein-1 (MCP-1) [16–19]. Resveratrol also prevents platelet activation by modulating platelet adhesion,

secretion and activation signaling, ROS production, and apoptosis and by enhancing nitric oxide (NO) production [20–22]. Furthermore, several studies demonstrated that resveratrol inhibits protein kinase C (PKC) activation and intracellular calcium release, thus blocking phosphoinositide metabolism upstream platelet activation signaling [23].

2.2. Hypertension: Preclinical Studies. The “antihypertensive” effect of resveratrol is thought to be mediated by both endothelium-dependent and endothelium-independent mechanisms [24, 25], by inhibition of vascular smooth muscle cell (VSMC) contractility, by reduction of vasoconstrictor molecules expression (angiotensin (Ang) II and endothelin (ET)-1), and by inhibition of strain-induced ET-1 gene expression through the extracellular-signal regulated kinase (ERK) 1/2 pathway [11, 26, 27]. Finally, its effect on the sympathetic nervous system (SNS) can also contribute to blood pressure (BP) lowering [28]. The antihypertensive effect of resveratrol (administered at the dose of 10–320 mg/kg body weight/day) has been demonstrated, although with some controversial results, in several hypertensive animal models, including spontaneously hypertensive (SHR), two kidney one-clip hypertensive, partially nephrectomized, and deoxycorticosterone acetate- (DOCA-) salt hypertensive rat models, and in the Ang II-infused mouse [11, 29–32]. Controversies appear mainly related to the specific model under study. In particular, resveratrol was more effective in lowering BP in animals with either diabetes or metabolic syndrome in which variable doses of resveratrol (20 mg/kg/day) were administered [33].

Along with the antihypertensive effect, an improvement of endothelial function was described, being largely attributable to endothelial NO synthase (eNOS) activation [34, 35]. This effect can certainly contribute to protecting vasculature from hypertensive damage [36].

2.2.1. Hypertension: Clinical Studies. Scarce information is available regarding the antihypertensive effect of resveratrol in humans. A recent meta-analysis has shown that treatment with ≥ 150 mg/day of resveratrol, considered as a very low dose, decreases systolic BP (SBP) without affecting diastolic BP (DBP) [37]. Interestingly, doses of 12,5–100 μ L of resveratrol were shown to enhance Acetylcholine-mediated vasorelaxation in blood vessels from patients with hypertension and dyslipidemia but not in vessels from healthy subjects [38]. Although resveratrol supplementation did not exert any effect on BP in healthy obese adults and in patients with metabolic syndrome, it significantly improved flow-mediated dilatation (FMD) in these subjects [37, 39]. Similar results were obtained in patients with previous myocardial infarction (MI) receiving 10 mg of resveratrol daily for 3 months [40]. However, the duration of these clinical trials was too short in order to assess the long-term consequences of the dietary intervention.

No clinical trials are available yet exploring the BP lowering effect of resveratrol in hypertensive patients.

2.3. Atherosclerosis and Dyslipidemia: Preclinical Studies. Resveratrol acts at the very early stages of atherosclerosis

by increasing the hepatic uptake of low-density lipoprotein (LDL) through an AMPK independent mechanism and by reducing the expression of *intercellular adhesion molecule-1* (ICAM-1) and of vascular cell adhesion molecule-1 (VCAM-1) on endothelium [41, 42]. Additional in vitro studies demonstrated that resveratrol, likely via the phosphatidylinositol 3'-kinase (PI3K)/protein kinase B (PKB or Akt) pathway, blunts MCP-1 and chemokine receptor type 2 expression in monocytes [43, 44]. Also, it reduces foam cell formation by upregulating the expression of cholesterol transporters and by downregulating the uptake of oxidized LDL (Ox-LDL) [45]. The anti-inflammatory and antioxidant properties of resveratrol may be responsible for inhibition of LDL oxidation, of macrophage migration and transformation into foam cells, as well as of VSMCs migration and proliferation [46, 47].

Several in vivo studies have shown the hypocholesterolemic effect of a standard dose of resveratrol (20 mg/kg/day) [48, 49]. In the apolipoprotein (APO) E^{-/-} mice, resveratrol downregulated the hepatic 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase enzyme, a key enzyme involved in cholesterol biosynthesis, thus reducing total and LDL cholesterol and increasing high-density lipoprotein (HDL) cholesterol [50]. In the high fat fed mice, resveratrol increased liver expression of cholesterol 7 α -hydroxylase (CYP7A1) which led to increased bile acid synthesis and secretion, thus lowering the plasma level of total and LDL cholesterol [51].

2.3.1. Atherosclerosis and Dyslipidemia: Clinical Studies. A meta-analysis evaluating the benefits of resveratrol supplementation on plasma lipids revealed no significant effect on any of the lipid parameters (e.g., total LDL and HD-cholesterol and triglycerides) independently of the dose, duration of the study, and cardiovascular risk of the considered population [52]. However, few single studies included in this meta-analysis reported that a relatively low dose of resveratrol treatment (250 mg per day for 3 months) led to a significant decrease of total cholesterol, total and ox-LDL, and ApoB levels in patients with type 2 diabetes mellitus (T2DM), coronary artery disease (CAD), hyperlipidemia, and other cardiovascular risk factors [53]. Similarly, total cholesterol and triglyceride levels were reduced by a very low dose of resveratrol (20 mg/per day for 2 months) in patients with stable angina [54].

2.4. Obesity and T2DM: Preclinical Studies. Resveratrol reduced lipid accumulation both in vivo and in vitro by inhibiting lipogenesis, increasing apoptosis, and promoting lipolysis [55–57]. In Sprague-Dawley rats the body fat-lowering effect of 30 mg resveratrol/kg body weight/day was mediated, at least, in part, by reduction in fatty acid uptake from circulating triacylglycerols, as well as by a de novo lipogenesis in adipose tissue [58]. In addition, it modulated insulin signaling pathway and improved insulin sensitivity in adipose and muscle tissue, as well as glucose uptake and insulin secretion [59, 60]. In human muscle cells derived from T2DM patients, resveratrol may improve glucose utilization and resistance to hyperglycemia by inhibiting phosphorylation of Insulin Receptor Substrate-1 [61].

In vivo, resveratrol restores vascular function through antioxidant, anti-inflammatory, and antiapoptotic properties, as it was observed treating rats with very low doses (0,75 mg/kg/three times a day) [62]. At a standard dose of 20 mg/kg/day, it improved cardiac function in both type 1 and type 2 DM [63–65].

2.4.1. Obesity and T2DM: Clinical Studies. Resveratrol, at the standard dosage of 500 mg three times a day, improved insulin sensitivity in both obese and metabolic syndrome patients [66, 67]. However, other studies failed to confirm these findings [68, 69]. Anti-inflammatory effects of resveratrol were reported in several clinical studies performed in patients with high cardiovascular risk profile [54, 70]. Administration of resveratrol using different chemical formulae at several dosages was associated with decreased oxidative stress in patients with metabolic syndrome [71].

2.5. Ischemic Heart Disease: Preclinical Studies. Resveratrol protects against ischemic heart disease through multiple mechanisms. The mechanisms underlying the preconditioning effect of resveratrol (0,5 mg/kg/day) appear to be mainly mediated by NO and the antioxidant enzyme heme oxygenase-1 (HO-1) [72].

In vitro studies showed that resveratrol upregulated vascular endothelial growth factor (VEGF) expression in cardiomyocytes and in ECs through an increased oxidative-stress related proteins Thioredoxin-1 (Trx-1) and HO-1 expression [73]. It also protected cardiac tissue from cell death through multiple mechanisms including antiapoptotic effects and autophagy [74, 75].

Pretreatment of rats with resveratrol resulted in cardioprotection when the isolated heart was subjected to 30 min global ischemia followed by 2 hr reperfusion, or following permanent left anterior descending coronary artery (LAD) occlusion [76]. Resveratrol can potentiate regeneration of infarcted myocardium in a LAD occlusion rat model by stimulating neovascularization and cardiac stem cells [76, 77]. Interestingly, pretreatment with resveratrol largely restored the altered microRNAs expression in the ischemic heart [78].

The protective effects of resveratrol in the ischemic myocardium were confirmed in vivo [72, 79]. An interesting study conducted by Kanamori et al. suggested that only high dose (50 mg/kg/day) of resveratrol may be an effective treatment for ischemic heart failure (HF) by preventing necrotic area expansion and by improving cardiac function. Authors tested two doses of resveratrol (5 mg/kg and 50 mg/kg) demonstrating the dose-dependent effect of this compound [80].

2.5.1. Ischemic Heart Disease: Clinical Studies. Few clinical trials investigated the effects of both standard and low doses of resveratrol in stable angina, acute coronary syndromes, and previous MI with positive results [40, 54, 70]. Additional studies suggested that resveratrol may be cardioprotective through increase of adiponectin and reduction of thrombogenic plasminogen activator inhibitor type 1 (PAI-1) [81, 82].

2.6. Cardiac Hypertrophy and Heart Failure: Preclinical Studies. Resveratrol was shown to prevent cardiac hypertrophy and dysfunction through reduction of oxidative stress, inhibition of hypertrophic gene expression, and increase of Ca^{2+} handling [83]. The antihypertrophic effect of resveratrol may be BP independent. For instance, low doses of resveratrol (2.5 mg/kg/day) prevented cardiac hypertrophy without reducing BP in SHR and Dahl-salt sensitive rats [84, 85]. The cardioprotective properties were demonstrated in several animal models, including pressure-overload, volume overload, SHR, doxorubicin-induced cardiotoxicity, myocarditis, MI, and ischemia-reperfusion (I/R) injury [15, 84, 86–90]. Recently, Sung et al. demonstrated that high doses of resveratrol (320 mg/kg/day) promote beneficial remodeling and improve both diastolic function and cardiac energy metabolism in a mice model of pressure-overload HF, thus increasing animal survival [91].

2.6.1. Cardiac Hypertrophy and Heart Failure: Clinical Studies. In one study, performed in patients with HF of ischemic origin, treatment with resveratrol significantly improved diastolic function and induced a modest increase of systolic performance, despite the low dose administered (10 mg of resveratrol capsule/day) [40].

2.7. Cerebrovascular Disease: Preclinical Studies. The previously described beneficial vascular properties of resveratrol can also explain protection from ischemic stroke [92]. In vitro resveratrol promoted angiogenesis in cerebral ECs and prevented impairment of eNOS-dependent vasorelaxation of cerebral arterioles in diabetes [93, 94]. It also reduced infarct size in a rat model of focal cerebral ischemia and preserved blood brain barrier function by interfering with occludin and zonula occludens- (ZO-)1 tight junctions [92, 95, 96]. The stroke protective effects of resveratrol were also attributed to its specific neuroprotective properties [97, 98].

2.7.1. Cerebrovascular Disease: Clinical Studies. There are no clinical studies investigating the protective effects of resveratrol in stroke patients. Interestingly, a single dose (250 mg) of *trans*-resveratrol increased cerebral blood flow during a mental stress (cognitive tasks) in healthy adult subjects [99].

2.8. Other Cardiovascular Diseases: Preclinical Studies. Resveratrol protected from doxorubicin-induced cardiotoxicity in a variety of animal models through the above discussed mechanisms [100–102]. However, there is scarce information on the cardioprotective effects of resveratrol in cancer patients treated with either doxorubicin or other cardiotoxic chemotherapeutic agents.

Few studies suggested an antiarrhythmic property. In fact, resveratrol caused a significant antiarrhythmic effect in three models of arrhythmia: aconitine-induced, ouabain-induced, and coronary ligation-induced arrhythmias [103]. Furthermore, chronic oral low-dose resveratrol treatment (5 mg/kg/day for 4 weeks starting one week before MI) significantly suppressed MI-induced ventricular tachycardia and ventricular fibrillation [104]. Recently, Baczkó et al.

designed and characterized a multifunctional resveratrol-derived small molecule, compound 1, targeting a number of key pathways involved in atrial fibrillation (AF), able to reduce the average and total AF duration in a model of inducible AF in conscious dogs [105].

3. *Brassica oleracea*

Brassica oleracea (BO) is a commonly used phytochemical. The species include broccoli, cauliflowers, Brussel sprouts, and kale. BO is highly enriched with bioactive molecules, whose effects on health have been partly explored [106–108]. It is known that the content of vitamin C varies significantly between the different subspecies of *Brassica*. These differences mainly depend on genotype and also on industrial storing, processing, and domestic cooking that reduce the final levels of available antioxidant compounds [109].

BO, in particular broccoli sprouts, is rich in glucosinolates: they are large molecules composed by a β -D-thioglucose group, a sulphonated oxime group and an amino-acidic side chain [110]. Sulforaphane is the active metabolite of glucoraphanin and is produced after hydrolyzation by myrosinase enzyme [111]. Cooking the vegetables partially denatures myrosinase; however, when glucoraphanin reaches the intestinal flora myrosinase-producing bacteria release the active metabolite that is then absorbed [112]. After absorption, sulforaphane is partly conjugated with glutathione in the liver, forming sulforaphane-glutathione. After reaching the kidneys, where it becomes sulforaphane-N-acetylcysteine, it is finally excreted in the urine [113]. Other active compounds of *Brassica* plants are anthocyanins, carotenoids, vitamin C, tocopherol, folic acid, and minerals. We will focus our discussion on sulforaphane and anthocyanins, as the main components of BO.

3.1. Molecular Targets and Properties. Molecular targets of BO include NF- κ B, nuclear factor-2 (Nrf2), mitogen-activated protein kinase (MAPK), c-Jun N-terminal kinase (JNK), Akt/PKB, and AMPK/SIRT-1/peroxisome proliferator-activated receptor- α (PPAR α)/uncoupling protein-2 (UCP2) [114–117]. By interacting with these molecular signaling pathways, BO plays antioxidant, anti-inflammatory, and antithrombotic effects.

3.2. Preclinical Studies. Broccoli sprouts exert several cardiovascular beneficial effects [106, 107].

With regard to glucosinolates, sulforaphane has been proven to be the most beneficial. In vitro, it induced expression of detoxification enzymes, the so called “ARE” targets (Antioxidant Response Elements: nicotinamide adenine dinucleotide (NADH) quinone reductase, HO-1, and glutathione transferase), and several nuclear factors, such as Nrf2, involved in ROS elimination and xenobiotic excretion [114]. Sulforaphane suppressed the expression of MAPK p38 in ECs through activation of Nrf2, thus leading to reduction of VCAM-1 synthesis [118]. By reducing ROS, sulforaphane lowered ox-LDL level in blood [119]. In a study conducted in rats fed for 14 weeks with 200 mg/day of dried broccoli sprouts, a significant increase in glutathione content was observed along with increased glutathione reductase and

peroxidase (GPx) activities in both heart and kidneys [120]. Interestingly, administration of broccoli sprouts in pregnant female stroke prone-SHR (SHRSP) decreased oxidative stress and BP levels, compared to females fed with control diet. Furthermore, offspring of females maintained on broccoli diet during pregnancy had also lower BP and tissue inflammation in adulthood, regardless of diet [121].

Anthocyanins are known to promote optimal platelet function and antithrombotic effects [122]. These compounds can act on different types of cells involved in atherosclerosis development. In fact, they exert a protective effect toward TNF- α induced MCP-1 secretion in primary human ECs [123]. Anthocyanins prevented the expression of VEGF stimulated by platelet derived growth factor (PDGF) AB in VSMCs and by MAPK p38 and c-JNK inhibition [115]. Moreover, anthocyanins extract induced endothelium-dependent relaxation in porcine coronary arteries [124]. Increased cardiac glutathione concentrations in rats receiving long-term administration of anthocyanins contributed to the antioxidant effects [125]. The protective effect on heart also depends on reduction of hypertrophy-associated increased phosphorylation of PKC and on activation of Akt/PKB [116]. Moreover, anthocyanins prevented CD40-activated proinflammatory signaling in ECs by regulating cholesterol distribution [126]. They also inhibit the activation of NF- κ B and lipopolysaccharides induced NO biosynthesis in macrophages [127].

Broccoli sprouts protect from myocardial oxidative damage and cell death in ischemia/reperfusion (I/R) rat models. In particular, anthocyanins decreased the extent of cell death in cultured cardiomyocytes and reduced infarct size by inhibiting signal transducer and activator of transcription 1 (STAT1) stimulation [106, 128]. Notably, BO improved diabetic nephropathy in rats [107] and prevented renal damage in salt-loaded SHRSP, independently from SBP, through AMPK/SIRT1/PPAR α /UCP2 axis activation [117]. In fact, selective inhibition of PPAR α antagonized the nephroprotective effects of BO sprouts, consistently with previous evidence on the role of cyanidin as PPAR α agonist [129].

3.3. Clinical Studies. The beneficial effects in humans were enhanced when broccoli supplements were combined with fresh broccoli sprouts administration in healthy subjects who consumed either 68 gr of broccoli sprouts or 6 Brocco-Max pills (about 3 gr of freeze-dried broccoli sprouts in 6 pills) for 7 days [130, 131]. In a small clinical trial conducted in 6 men and 6 women, all smokers, eating 100 gr of broccoli sprouts daily for 7 days, a significant reduction of both total and LDL cholesterol along with urinary 8-isoprostanes and other markers of oxidative stress was observed [119]. The administration of 150 mL/day kale juice for 12 weeks in 32 men with hypercholesterolemia significantly reduced plasma LDL cholesterol and increased both HDL cholesterol and GPx activity, thus lowering CAD risk [108]. In addition, broccoli sprouts supplement could play favorable effects on lipid profiles and OX-LDL/LDL cholesterol ratio in T2DM [132]. Recently, anthocyanins intake (8,4–23,6 mg/day) was shown to associate with lower arterial stiffness and central BP in women [133].

Results from human trials are controversial. In fact, Curtis et al. showed no effect on markers of CVDs (including inflammatory biomarkers, platelet reactivity, lipids, and glucose), on liver and kidney function, as well as on anthropometric parameters, BP, and heart rate, following 12-week intervention with 500 mg/day cyanidin in postmenopausal women [134].

4. Curcumin

Curcumin (diferuloylmethane) is a naturally occurring phenolic compound isolated as a yellow pigment from spice turmeric (*Curcuma Longa*). This compound has received attention due to its various biological and pharmacological activities. Its therapeutic effects have been extensively investigated, particularly in the treatment of cancer and inflammatory diseases [135].

There is growing evidence that curcumin has a potential role in protection from several CVDs [135, 136].

4.1. Molecular Targets and Properties. Curcumin interacts with different molecular targets, such as Janus Kinase 2 (JAK2)/STAT3, AMPK/UCP2, Akt/Nrf2, ERK, MAPK p38, JNK, ICAM-1, MCP-1, and IL-8 [137–141]. As a consequence, it exerts anti-inflammatory, antiplatelet, and antioxidant properties [141–144]. Concerning the latter, a single dose of 15 mg/kg of curcumin appears to decrease levels of xanthine oxidase, superoxide anion, lipid peroxides, and myeloperoxidase and to increase levels of SOD, catalase, GPx, and glutathione-S-transferase (GST) [145]. Moreover, this phytochemical reduces level of eNOS and iNOS through the activation of NF- κ B and protein-1 (AP-1) [146]. Curcumin is also a potent inducer of HO-1 in ECs through activation of ARE in several cardiovascular cells exposed to curcumin 5–15 μ M [147]. Moreover, curcumin appears to attenuate mitochondrial alterations and respiratory cellular dysfunction [148].

4.2. Preclinical Studies. Curcumin plays a protective role on endothelium by inducing HO-1 in bovine aortic ECs [147]. It exerts antiproliferative and antiapoptotic effects on VSMCs, exposed to 1–25 μ M of curcumin, thus attenuating carotid artery neointima formation [149–151]. It plays a relevant role on calcium homeostasis in both skeletal muscle and cardiac sarcoplasmic reticulum [152].

The role of curcumin in CVDs has been investigated in several animal models. For instance, 1,66 mg curcumin/kg showed a hypolipidemic effect and protection from aortic fatty streak development [153, 154]. The cardioprotective role of curcumin was shown in myocardial ischemia rat models [145, 155]. In I/R models, curcumin reduced collagen synthesis and fibrosis and significantly improved left ventricular end-diastolic volume, stroke volume, and ejection fraction [156]. In addition, it reduced MI size and depressed lactate dehydrogenase release in the coronary blood flow through activation of JAK2/STAT3 [137]. These beneficial effects could be related to a decrease of proinflammatory cytokines and of cardiomyocyte apoptosis [157].

In two different HF models, 50 mg curcumin/kg/day ameliorated systolic function and prevented myocardial hypertrophy by inhibiting p300-HAT (histone acetyltransferases) [158]. Additionally, a larger amount of curcumin (200 mg/kg/day) showed a protective role in adriamycin-induced cardiac damage [159] and it also prevented cardiovascular complications in diabetes [146]. In fact, it reduced high glucose-induced overexpression of inflammatory cytokines in macrophages [144]. A beneficial role toward myocardial injury was reported in renal I/R injury rat models [160].

Finally, a standard dose of curcumin (25–50 mg/kg/day) protected against cerebral ischemic insult [161], as well as aging-related cerebrovascular dysfunction via AMPK/UCP2 pathway. It protected neurons against ischemic injury through Akt/Nrf2 pathway [138, 139]. In different stroke models curcumin not only decreased oxidative stress but also attenuated reperfusion injury by preventing neutrophil adhesion to the cerebrovascular microcirculation [162, 163].

4.3. Clinical Studies. Controversial results exist with regard to the effect of curcumin on plasma lipids in healthy subjects. In fact, in healthy volunteers, a dosage of 500 mg curcumin/day decreased both serum lipid peroxides and total cholesterol and increased HDL cholesterol [164]. Hypolipidemic effects were also observed in patients affected by atherosclerosis, acute coronary syndrome, and T2DM. Moreover, the effect of curcumin administration on lipid profile was evaluated in acute coronary syndrome (ACS) patients at escalating doses (low dose, 3 times 15 mg/day; moderate dose, 3 times 30 mg/day; high dose, 3 times 60 mg/day). Unexpectedly, this study showed that the low dose of curcumin was associated with higher reduction of total, HDL and LDL cholesterol levels [165, 166]. On the other hand, a meta-analysis failed to show protective effects of curcumin on both cholesterol and triglycerides in a heterogeneous population [167]. Curcumin administration and aerobic exercise training increased FMD in postmenopausal women [168]. Interestingly, curcumin may improve the blood compatibility of rapamycin-eluting stents through its antiplatelet properties [169].

5. Berberine

Berberine (BBR), an alkaloid isolated from *Hydrastis canadensis*, the Chinese herb Huanglian, and many other plants, such as the Berberidaceae and Ranunculaceae families, has a long history in traditional Chinese medicine. BBR is present in roots, rhizomes, and stem bulk of the plants. Various pharmacological actions, including antibiotic, immunostimulant, antitumor, and antimotility properties have been described for BBR [170, 171].

Recent studies have indicated that BBR may be also effective in treating chronic, multifactorial diseases, including diabetes, hyperlipidemia, heart diseases, cancer, neurological disorders, and inflammatory diseases [172, 173].

5.1. Molecular Targets and Properties. Molecular mechanisms mediating antioxidant effects appear to be mainly related

to upregulation of both SOD and UCP2 and to down-regulation of NADPH oxidase expression [174, 175] with particular regard to NADPH oxidase 2/4 subunits [175]. BBR administration activates Nrf2 pathway, which is crucial for antioxidant and anti-inflammatory activities [176]. BBR could suppress inflammation by blocking the MAPK pathways in a AMPK-dependent manner, by inhibiting the NF- κ B signaling pathway and the Rho GTPase pathway and by attenuating transcription activity of AP-1, which is possibly mediated by PPAR α activation [177–179].

5.2. Preclinical Evidences. In vitro studies demonstrated the role of BBR in counteracting endothelial progenitor cells (EPCs) dysfunction. In fact, BBR improved the proliferative ability of EPCs impaired by TNF- α via activation of PI3K/Akt/eNOS signaling pathway [180]. Moreover, BBR induced endothelium-dependent vasorelaxation and enhanced endothelium-independent VSMC dilatation through a partial reduction of oxidative stress [181].

In VSMCs, isolated from thoracic aorta of Sprague-Dawley rats, BBR inhibited Ang II- and heparin binding epidermal growth factor- (HB-EGF-) induced VSMC proliferation and migration. In vivo results showed a reduction of neointima formation after balloon injury, thus lowering risk of restenosis [182]. Zimetti et al. demonstrated a double protective effect of BBR on cholesterol homeostasis underlying foam cells formation and on the inflammatory phenotype in mouse and human macrophages [183].

BBR affected glucose metabolism by increasing insulin secretion, stimulating glycolysis, suppressing adipogenesis, and increasing glucokinase activity and both glucose transporter-4 (GLUT-4) and glucagon-like peptide (GLP-1) levels in glucose-consuming tissues [184].

Furthermore, BBR was shown to have lipid-lowering properties in animals as well as in hyperlipidemic patients through mechanisms different from those of statins, involving activation of ERK pathway and increase of LDLR expression on the hepatocytes surface [185]. Interestingly, contrasting results were reported with regard to modulation of the gene encoding proprotein convertase subtilisin kexin 9 (PCSK9), a natural inhibitor of LDLR. In HepG2 cells 20 μ M BBR downregulated the transcription of the gene [186], whereas 400 mg BBR/kg/day significantly reduced body weight and improved lipid profile by increasing the PCSK9 expression levels through Sterol Regulatory Element-Binding Proteins activation in the high fat diet (HFD) rat model [187].

BBR, at the dosage of 100 mg/kg/day, plays positive inotropic, antiarrhythmic, and vasodilator properties related to the cardiovascular system [188, 189]. The antiarrhythmic effects are due, at least in part, to preferential blockade of the components of the delayed rectifying potassium current, I(Kr), and I(Ks) and to increased effective refractory period of Purkinje fibers [190, 191].

The beneficial effects of BBR were demonstrated in several animal models such as SHR, HFD rats, pressure-overload HF, and myocardial ischemia [187, 192–194]. Notably, 50 Sprague-Dawley rats were treated with BBR (30 or 60 mg/kg) demonstrating that BBR had cardioprotective effects against

acute ischemic myocardial injury in a dose-dependent manner [194]. BBR counteracted several pathological features of hypertension, including suppression of endoplasmic reticulum stress, inhibition of ROS accumulation, and attenuation of endothelium-dependent contractions in SHR [195]. The antihypertensive effect of BBR derivative 6-protoberberine (PTB-6) was shown in conscious SHR and Wistar-Kyoto (WKY) rats, and it was mediated by reduced SNS activity through a negative inotropic and chronotropic effect [192].

A recent in vivo study reported that BBR can prevent cardiac hypertrophy and attenuate cardiomyocyte apoptosis in the transverse aortic contraction treated rat model [193].

In a rat model of MI, BBR administration significantly enhanced autophagic activity, attenuated adverse left ventricular remodelling, and preserved left ventricular systolic function. Interestingly, low-dose BBR (10 mg/kg per day) was associated with greater improvement in cardiac function compared with high-dose BBR (50 mg/kg per day) [196]. In diabetic rat models, BBR protected the heart against I/R injury, improved cardiac function, and reduced myocardial apoptosis via activation of AMPK and PI3K/Akt and eNOS signaling [197]. In addition, cardioprotective effects of BBR in myocardial ischemia are due to its antioxidant and anti-inflammatory properties [194].

Chronic administration of BBR significantly reduced oxidative stress and vascular inflammation and suppressed atherogenesis in ApoE^{-/-} mice by AMPK-dependent UCP2 expression [174].

In a middle cerebral artery occlusion (MCAO) model, BBR improved neurological outcome and reduced I/R-induced cerebral infarction 48 hrs after MCAO. The protective effect of BBR was confirmed in vitro [198].

5.3. Clinical Evidences. BBR has shown good safety results in human studies [199]. A randomized clinical trial tested its effects in 156 patients with chronic congestive HF. The BBR-treated group (1,2–2 gr/day) showed significantly greater increases in left ventricular ejection fraction and exercise capacity, significant improvements on the dyspnea-fatigue index, and decreased rates of ventricular premature complexes and long-term mortality [200].

Treatment of 100 arrhythmic patients with BBR resulted in a >89% reduction in premature beating in the majority of patients and >50% reduction in the remaining patients [201]. These results were independently reproduced [202]. A recent meta-analysis, including 11 randomized controlled studies (874 Chinese participants affected by hyperlipidemia, T2DM, or both diseases), has shown a significant reduction in total cholesterol, triglycerides, and LDL cholesterol levels and a small but significant increase in HDL cholesterol [203].

In T2DM patients, high-dose BBR administration (100–200 mg/kg/day) was associated with a significant reduction in glycated hemoglobin, fasting plasma insulin, postprandial glucose, and fasting plasma glucose [204].

BBR beneficial effects were also observed in hypercholesterolemic European patients [205].

A recent meta-analysis emphasized the role of BBR in the treatment of hypertension. In fact, BBR associated with

TABLE 1: Preclinical effects of vegetable compounds.

Vegetable	Preclinical effects	Reference
	(i) Upregulates the antioxidant system and reduces ROS production (ii) Inhibits vascular inflammation and prevents platelet activation (iii) Lowers BP in animals with either diabetes or metabolic syndrome (iv) Inhibits very early stages of atherosclerosis (v) Reduces lipid accumulation by inhibiting lipogenesis, increasing apoptosis, and promoting lipolysis (vi) Protects against ischemic heart disease (vii) Protects cardiac tissue from cell death through apoptosis and autophagy (viii) Potentiates regeneration of infarcted myocardium (ix) Prevents cardiac hypertrophy and dysfunction (x) Promotes angiogenesis in cerebral ECs and prevents impairment of eNOS-dependent vasorelaxation of cerebral arterioles (xi) Protects from doxorubicin-induced cardiotoxicity (xii) Antiarrhythmic effects	[14, 15] [16–22] [33] [41, 42] [55–57] [72] [74, 75] [76, 77] [83] [93, 94] [100–102] [103]
Resveratrol	(i) Induces expression of detoxification enzymes (ARE targets) (ii) Lowers ox-LDL blood levels (iii) Decreases oxidative stress and BP levels in pregnant female SHRSP (iv) Promotes optimal platelet function and antithrombotic effects (v) Acts on different types of cells involved in atherosclerosis development (vi) Regulates cholesterol distribution (vii) Protects from myocardial oxidative damage and cell death in ischemia-reperfusion rat models (viii) Nephroprotective effects	[114] [119] [121] [122] [123] [126] [106, 128] [129]
<i>Brassica oleracea</i>	(i) Protective role on endothelium by inducing HO-1 (ii) Antiproliferative and antiapoptotic effects on VSMCs, attenuating neointima formation (iii) Hypolipidemic effect and protection from aortic fatty streak development (iv) Reduces collagen synthesis and fibrosis and improves left ventricular end-diastolic volume, stroke volume, and ejection fraction (v) Reduces MI size (vi) Protects from adriamycin-induced cardiotoxicity (vii) Protects from cerebral ischemic insult	[147] [149–151] [153, 154] [156] [137] [159] [138, 139]
Curcumin	(i) Improves the proliferative ability of EPCs (ii) Induces endothelial-dependent vasorelaxation and enhances endothelium-independent VSMC dilatation (iii) Inhibits VSMC proliferation and migration and reduces neointima formation (iv) Lipid-lowering properties (v) Positive inotropic, antiarrhythmic, and vasodilator properties (vi) Antihypertensive effects in SHR (vii) Prevents cardiac hypertrophy and attenuates cardiomyocyte apoptosis (viii) Attenuates adverse left ventricular remodeling and preserves left ventricular systolic function in rat model of MI	[180] [181] [182] [185] [188, 189] [195] [193] [196]

ROS: reactive oxygen species; BP: blood pressure; eNOS: endothelial nitric oxide synthase; ARE: Antioxidant Response Elements; ox-LDL: oxidized low-density lipoprotein; SHRSP: stroke prone spontaneously hypertensive rats; HO-1: heme oxygenase-1; ECs: endothelial cells; VSMC: vascular smooth muscular cells; MI: myocardial infarction; EPCs: endothelial progenitor cells.

TABLE 2: Clinical effects of vegetable compounds.

Vegetable	Clinical effects	Reference
Resveratrol	(i) Decreases SBP without affecting DBP	[37]
	(ii) Enhances Ach-mediated vasorelaxation in hypertensive and dyslipidemic pts	[38]
	(iii) Improves FMD in pts with either metabolic syndrome or previous MI	[39, 40]
	(iv) Decreases total cholesterol and ox-LDL , triglycerides , and ApoB levels in pts with T2DM, CAD, hyperlipidemia, and other CV risk factors	[53, 54]
	(v) Improves insulin sensitivity in both obese and metabolic syndrome pts	[66, 67]
	(vi) Improves significantly diastolic function and modestly systolic function in pts with previous MI	[40]
<i>Brassica oleracea</i>	(i) Reduces total , LDL cholesterol and markers of oxidative stress in smokers and hypercholesterolemic pts	[108, 119]
	(ii) Improves lipid profiles and ox-LDL/LDL cholesterol ratio in T2DM pts	[132]
	(iii) Lowers arterial stiffness and central BP in women	[133]
Curcumin	(i) Decreases both total and LDL cholesterol and increases HDL cholesterol in healthy subjects and in ACS pts	[164, 165]
	(ii) Increases FMD in postmenopausal women	[168]
Berberine	(i) Increases both LVEF and exercise capacity and decreases rates of ventricular premature complexes and long-term mortality in HF pts	[199]
	(ii) Reduces total cholesterol , triglycerides , and LDL cholesterol levels and modestly increases HDL cholesterol in hyperlipidemic and T2DM pts	[203, 205]
	(iii) Reduces glycated hemoglobin , fasting plasma insulin , postprandial glucose , and fasting plasma glucose in T2DM pts	[204]
	(iv) Lowers SBP and DBP in hypertensive, T2DM, and hyperlipidemic pts	[206]

SBP: systolic blood pressure; DBP: diastolic blood pressure; Ach: Acetylcholine; FMD: flow-mediated dilation; MI: myocardial infarction; ox-LDL: oxidized low-density lipoprotein; HDL: high-density lipoprotein; Apo: apolipoprotein; T2DM: type 2 diabetes mellitus; CAD: coronary artery disease; CV: cardiovascular; ACS: acute coronary syndrome; LVEF: left ventricular ejection fraction; HF: heart failure; pts: patients.

lifestyle intervention tended to lower the level of BP more than lifestyle intervention alone or than placebo [206].

6. Conclusions

Preclinical studies revealed several beneficial cardiovascular effects of resveratrol, *Brassica oleracea*, curcumin, and berberine. The benefits appeared to be mainly dependent on antioxidant, anti-inflammatory, and antithrombotic properties. In fact, the excellent results of both in vitro and in vivo studies induced researchers and clinicians to test the effects of phytochemicals in humans. However, evidences obtained from the few available clinical trials on the protective effects of these compounds in several CVDs are still controversial. A main limitation of current clinical studies relies on their heterogeneity and on small samples size. Furthermore, based on the literature discussed in the present paper, some confusion arises about the precise dose of each compound exerting more pronounced beneficial effects. In particular, whereas the use of a very high dose is associated with the most protective effects for few phytochemicals, the lowest dose turns out to be the most effective for other compounds. This phenomenon appears to be related to different animal models as well as to the specific disease under consideration. Therefore, there is a need for additional larger and well controlled human studies.

Altogether, the lack of a clear beneficial role in humans, the wide variety of in vitro, ex vivo, and in vivo experimental evidences that are summarized in Tables 1 and 2, suggests that resveratrol, *Brassica oleracea*, curcumin, and berberine may reveal very useful preventive and/or therapeutic tools for the treatment of CVDs, as a valid support to medical therapies.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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