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Protective Activity of Resveratrol in Cardio- and Cerebrovascular Diseases

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Additional information is available at the end of the chapter

Abstract

Resveratrol (RSV) is a natural nonflavonoid polyphenol compound containing a stilbene structure similar to that of estrogen diethylstilbestrol. It is a fat-soluble compound existing in cis-, trans-, and piceid isomeric forms, isolated for the first time in 1940 from a plant used in traditional Chinese and Japanese medicine. Although initially used for cancer therapy, it has shown beneficial effects against most cardiovascular and cerebrovascular diseases. Its beneficial effects are mainly related to its antioxidant properties. Here, we review the metabolism and the ability of RSV to modulate redox signaling and to interact with multiple molecular targets of different intracellular pathways exerting protective effects against cardio-cerebrovascular diseases and metabolic disorders such as diabetes, reporting evidence in animal models and its efficacy and toxicity in humans. The aim of this chapter is to highlight the mechanisms, the biology, and the potential use of resveratrol to prevent, protect and aid cardio- and cerebrovascular diseases.

Keywords: resveratrol, cardiovascular diseases, cerebrovascular diseases, molecular mechanisms, clinical effects, nitric oxide, oxidative stress

1. Introduction

Both in the scientific world and in the public opinion, a particular attention is paid to cardiovascular diseases since they represent the first cause of mortality in the Western world. The major risk factors are represented by different factors such as hyperlipidemia, arterial hypertension, diabetes and obesity, and the common anatomopathological basis is atherosclerosis. Since the early 50s of the last century, the pioneering studies of the American scientist

Ancel Keys have highlighted the enormous potential of proper nutrition in the prevention of cardiovascular diseases (CVDs). Since then, the interest in food science has been growing and was corroborated by the discovery of new associations between healthy nutrition and protection against other cardiovascular diseases, such as diabetes, hypertension, atherosclerosis and myocardial infarction. A clear and concise testimony of the work of the American scientist provides it in a recent article that M. Mancini and J. Stamler, certainly two scholars who in their respective countries, Italy and the United States, have contributed most to spread and develop Keys' theorems [1]. The legacy of Keys is fundamentally contained in the seven countries study (SCS), which he initiated and coordinated, in which it has unequivocally demonstrated through the study of different populations that a high intake of saturated fats causes an increase in blood cholesterol and risk mortality for CVDs and that the level of blood cholesterol correlates with the risk of CVDs. Years later, Keys' insights, which were validated by epidemiological population studies, are now validated and investigated at the cellular and molecular level.

In the context of the recognized benefits deriving from "healthy eating," the chemical components that are largely responsible for the protective effects of the diet are gradually being highlighted. The importance of diet in the prevention of vascular diseases and dysfunction is highlighted by the observation that the incidence of certain diseases varies from country to country, where there are different eating habits. In vitro and in vivo studies have shown that some components of the diet, including vitamin E, vitamin C, retinoic acid, carotenoids such as lycopene (a powerful antioxidant in tomato) and polyphenols show a protective effect on the onset of CVDs [2].

On this regard, polyphenols are compounds that own one or more aromatic rings, with one or more hydroxyl groups and are generally classified as phenolic acids, flavonoids, stilbenes, coumarin, and tannins. Polyphenols are products of the secondary metabolism of plants, whose function is to protect the plant from the pathogenic attacks of parasites and also contribute to giving color to the plants [3]. Polyphenols have different structures, but all have aromatic rings, with one or more hydroxyl substituents; due to their structure, they are able to chelate metal ions and have the activity of scavengers of free radicals; they are also able to inhibit inflammation and platelet aggregation, thus exerting a protective action on the vascular system. Due to the acid character of the hydroxyl groups and the nucleophilic properties of the phenolic rings, the flavonoids are highly reactive and appear to have antiviral, antibacterial, immunostimulatory, anti-ischemic, antineoplastic, anti-inflammatory and gastroprotective properties. Flavonoids inhibit the activity of many enzymes including lipoxygenase, cyclooxygenase, monooxygenase, xanthine oxidase, NADPH-oxidase, phospholipase A2, some protein kinases and transcription factors such as NF-kB [4].

Among the flavonoids, resveratrol (3,5,4'-trihydroxystilbene) has attracted considerable attention from the scientific community. It belongs to the stilbenes family. The stilbenes (C6-C2-C6) are low molecular weight phenolic compounds, characterized by the presence of two aromatic rings joined by an ethane or an ethylene bridge. Resveratrol (RSV) (trans-3,4,5'-trihydroxystilbene) is a natural phytoalexin synthesized in response to fungal attacks, or to abiotic agents such as exposure to ultraviolet rays. Present in the peel of grapes and in

red wine, RSV has a wide variety of pharmacological properties [5]. Since its first isolation in 1940 by Takaoka, RSV has been associated with many properties [6]. Above all, the detection of RSV in wine has greatly contributed to finding the cardioprotective effects of this compound. This is testified by the so-called "French paradox," in which despite equal CVD risk factors, French population has a lower mortality rate compared to western countries [7]. This discovery about 25 years ago gave rise to an increasingly compelling urge to research all the mechanisms lying behind RSV and its beneficial effects [8]. This, unfortunately, gave also birth to a "red wine/RSV dogma," hence the concept that red wine benefits are due to its content in highly bioactive RSV. This concept might seem logic at first, as red wine is the main RSV dietary source; however, RSV content in wine is greatly variable and usually low, so its effects are mostly unpredictable and so its biological benefits are rather overestimated [7, 9–11]. Besides this noteworthy mention, consumption of red wine has been associated with beneficial effects on both the healthy and in patients with the previous acute coronary syndrome in terms of reduction in oxidative stress and endothelial function improvement [12, 13]. Other studies have shown that moderate consumption of red wine on man produces a reduction in risk factors for atherosclerosis. In red wine consumers, in fact, a reduction in platelet aggregation leads to an increase in plasma levels of HDL-cholesterol (HDL, high-density lipoprotein, responsible for the disposal of excess cholesterol in the peripheral tissues) and to a more low oxidation of low-density lipoprotein (LDL); these events are associated with a minor formation of atherosclerotic plaques in blood vessels and, therefore, a reduction in cardiovascular events, which makes RSV a cardioprotective agent [14, 15]. RSV, like many phytoalexins, has many biological activities—inhibition of lipid peroxidation and platelet aggregation, and alteration of lipid metabolism—possesses anti-inflammatory activity, is an inhibitor of the damage induced by free radicals and exerts an important vasorelaxant effects in different vascular districts.

2. Resveratrol and cardiovascular diseases: molecular mechanisms

A human takes with the diet small amounts of stilbenes, but one of the most represented is RSV. It is absorbed more in the duodenum; studies conducted on mice, using labeled RSV, have detected, already after 3 h from the administration, the presence of this molecule in the brain, heart, lungs, spleen and testicles, and after 6 h the stay in the liver and kidneys. In plasma, however, its concentration is very low and of short half-life. Trans-RSV has several beneficial effects and can act at different levels such as cellular signals, enzymatic processes, apoptosis and gene expression [16, 17]. Being lipophilic, RSV binds preferentially to HDL, LDL and VLDL lipoproteins, protecting them from oxidation from ionic metals and removing copper ions from both LDL and arterial walls. It is transported in the bloodstream bound mainly to LDL, both as an intact molecule and as its metabolites: trans-RSV-3-O-glucuronide, cis-RSV-3-O-glucuronide and cis-RSV-3-O-glucoside [18]. It has been shown that about 75% of trans-RSV taken with red wine is absorbed by passive diffusion and only <1% is bioavailable in the liver and in the intestine. Despite its very low concentration and of short half-life after assumption, RSV exerts several beneficial effects in different CVDs (**Figure 1**).
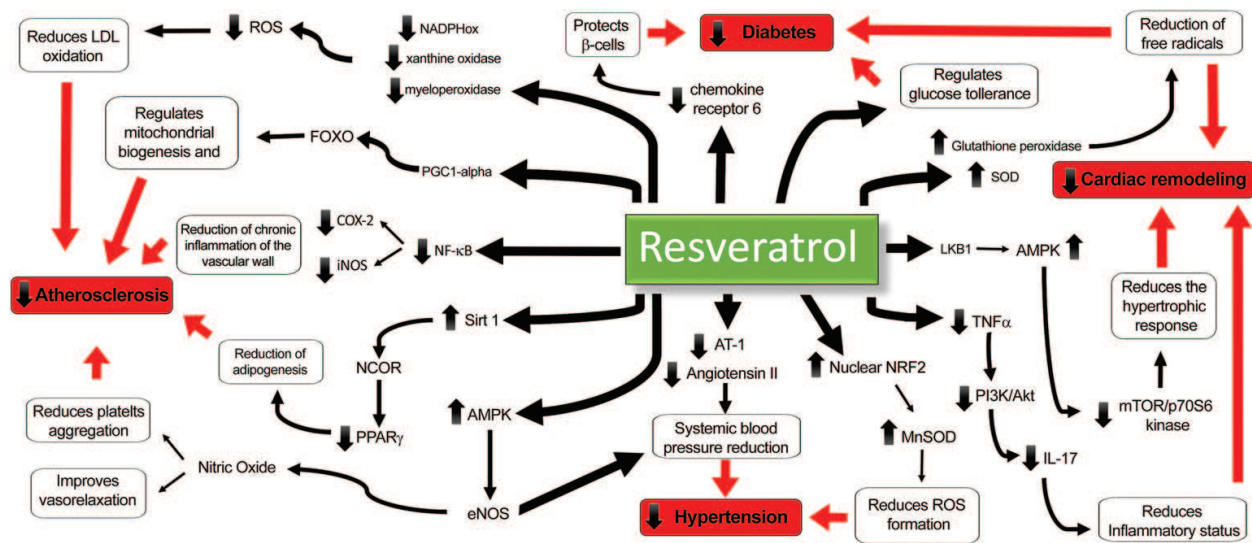
Figure 1. Schematic of molecular mechanisms of resveratrol in cardiovascular diseases.

2.1. Atherosclerosis

Atherosclerosis is a chronic inflammation of the vascular wall that results in the development of plaques and subsequent stenosis of the arteries [19]. A number of cytokines are involved in atherosclerosis-related inflammation; these include tumor necrosis factor alpha (TNF-α), interleukin (IL)-6 and monocyte chemoattractant protein-1 (MCP-1). These factors induce the expression of intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and E-selectin adhesion molecules and lipid homeostasis [20, 21]. Other important cytokines responsible for the cross-talk phenomenon that occurs between inflammatory cells and intrinsic factor wall cells are IL-1β and platelet-derived growth factor cross-reactive material [19]. Inflammation associated with atherosclerosis is mediated via the nuclear factor κB (NF-κB) signaling pathway, implying that substances inhibiting or activating this factor exert an important role in atherogenesis [22].

RSV is able to interfere with the activation of NF-kB, a transcription factor that regulates the expression of various genes involved in inflammation, cell proliferation and carcinogenesis such as COX2 cyclooxygenase and nitric oxide synthase (iNOS). Nitric oxide synthase maintains high concentrations of nitric oxide molecule able to exert vasodilatory effects, to inhibit adhesion and platelet aggregation and to block the cell growth and migration. Recently, it has been shown that RSV is an activator of sirtuins [23]. The sirtuins are a class of NAD-dependent deacetylases, implicated in the transcriptional modulation of the silencing of genes of the aging and cell survival processes. A large number of sirtuins appear to be involved in promoting longevity in mammals. RSV activates human sirtuin 1 (SIRT 1), a homolog of silencing information regulator 2 (SIR 2) of yeast [24]. SIRT 1 is involved in a multiplicity of cellular and metabolic events with a pivotal role in many of them. For example, it mobilizes fats from adipose tissue blocking the activity of peroxisome proliferator activated receptor-gamma (PPAR-gamma) receptors through its interaction with the NCOR nuclear receptor corepressor. Furthermore, it represses the transcriptional activity of the nuclear factor NF-kB by deacetylating the p65 subunit. SIRT 1 also modulates mitochondrial cell metabolism thanks

to the deacetylation performed on the PPAR-gamma receptor coactivator, PGC1 alpha and cell survival in stress conditions thanks to interaction with FOXO proteins. Moreover, it has been demonstrated that RSV is able to induce NOS-3 in direct and indirect manners through the 5'adenosine monophosphate-activated protein kinase (AMPK), SIRT1 and nuclear factor erythroid 2-related factor two pathways, thus modulating the vessels homeostasis [25].

In ApoE −/−/LDLR−/− mice, the lack of apolipoprotein E (ApoE) or LDL receptor (LDLR), and the over-expression of apolipoprotein B (ApoB) gene, leads to an increase in VLDL and LDL, contributing to the promotion of atherosclerosis [26]. In vivo studies in genetically hypercholesterolemic mice (ApoE−/−/LDLR−/−) and treated with oral administration of RSV in association with a high fat diet content have shown that the polyphenol suppresses the formation of atheroma in the aorta and reduces the laser-induced thrombosis in the carotid arteries [27], thus demonstrating the positive effect of RSV. An important antioxidant action of RSV is the inhibition of the oxidation of LDL; this inhibition is protective because the oxidative modification of LDL is considered a primary event in the pathogenesis of atherosclerosis. In fact, several studies have reported that oxidized LDL (ox-LDL) can stimulate platelet aggregation [28] and promote a procoagulant activity on the surface of human monocytes/macrophages, increasing the thromboplastin activity in the tissue [29]. Various enzymatic systems, present in endothelial cells and macrophages, are implicated in the oxidation of LDL. These systems include NADPH-oxidase, hypoxanthine/xanthine oxidase, myeloperoxidase (MPO) and the enzyme nitric oxide synthase (NOS) [30–32]. The products of these enzymes oxidize LDL, which alter endothelial cells, stimulate NADPH-oxidase, release pro-inflammatory cytokines and inhibit the endothelial enzyme nitric oxide synthase (eNOS) involved in the vasorelaxing activity [33]. RSV has been shown to act on these ROS scavenger enzymes by inhibiting the COX-2 cyclooxygenase and thus the expression of the scavenger receptor (SR-A) and inducing the vasorelaxing activity of eNOS [34]. It is well known that vascular smooth muscle cells (VSMCs) contribute to the pathogenesis of atherosclerotic lesions since their migration and proliferation are critical events for the progressive thickening in the intimate and development of atheroma in the vascular wall [35]. Several studies have shown that RSV can inhibit the proliferation of VSMCs [36, 37], induced by different mitogens such as serum, endothelin and PGDF. The antiproliferative effect of RSV is not mediated by the induction of apoptosis, but appears to be produced by the blockade of the G1-S transition of the cell cycle [38, 39] and of the synthesis of DNA [37]. These results suggest that RSV can selectively counteract the pathological proliferation of VSMCs in arterial walls in vivo and thus could exert an important protective effect on the onset of atherosclerosis.

2.2. Hypertension

Hypertension is one of the most important risk factors for cardiovascular diseases, representing the main causes of death in developed countries. It involves from 30 to 45% of the general population, with a tendency to increase incidence from the age of 50 and with an increase in prevalence in the most disadvantaged social classes [40].

The endothelial dysfunction is a hallmark of hypertension and clearly contributes to the onset and progression of the disease. It is important to underline that several risk factors for cardiovascular diseases can be effectively countered by a proper diet and by the intake of nutraceuticals.

On this regard, it has been demonstrated that RSV increases the levels of the vasodilator NO, which protects against the high blood pressure levels and subsequent cardiac hypertrophy and decreases ET-1 and angiotensin II (AngII) concentrations, which are associated with higher hypertension [41, 42]. In several animal models of hypertension, chronic RSV administration reduces systemic blood pressure in different rat models of hypertension [42, 43], suggesting the important beneficial effects evoked by polyphenol. RSV has also been shown to prevent remodeling of the mesenteric artery wall of spontaneously hypertensive rats (SHR), which is also typically observed in hypertensive humans, and to limit the increase in compliance of SHR arteries [44].

In another animal model of metabolic syndrome, the increased systolic blood pressure and reduced aortic eNOS expression were significantly improved by long-term administration of RSV. In the visceral adipose tissue (VAT) of this rat type, RSV treatment lowered tumor necrosis factor-alpha (TNF-α) production and increased the concentration of adiponectin, which improved the inflammatory status [45]. The development of pulmonary hypertension is induced by the proliferation of pulmonary arterial smooth muscle cells, endothelial dysfunction, oxidative stress, and inflammation. In monocrotaline-treated rats, RSV attenuated right ventricular systolic pressure, increased expression of endothelial NO synthase, decreased oxidative stress, and improved endothelial function in small pulmonary arteries. In addition, RSV was able to decrease expression of inflammatory cytokines, such as (TNF-α) and interleukin 6 (IL-6), and to limit leukocyte infiltration in the lung [46]. RSV also inhibited proliferation of pulmonary arterial smooth muscle cells. The increased level of NO induced by RSV is due to the augmentation of eNOS expression and activity [47]. It has been proposed that these effects involve SIRT1, which has been shown to directly deacetylate eNOS [48] leading to the improvement of nitric oxide production. It is well known that endothelial cells are responsible for the synthesis of ET-1, which is a strong vasoconstricting factor. RSV potentially inhibits stress-induced ET-1 gene expression, ET-1 mRNA levels, and ET-1 promoter activity by interfering with the ERK 1/2 pathway improving endothelial function through the decrease of ET-1 levels [49].

2.3. Cardiac remodeling

Chronic cardiovascular disease, such as hypertension, heart failure, or myocardial infarction, induces remodeling of the heart [50]. The remodeling process is characterized by hypertrophy of myocytes, hyperplasia of fibroblasts and vascular smooth muscle cells, excessive collagen deposition, and conduction abnormalities. As described above, RSV is able to prevent increased blood pressure in animal models; thus, it can protect the heart from structural remodeling (i.e., left ventricular hypertrophy, LVH) associated with pressure overload. Another antihypertrophic mechanism of RSV is via AMPK and its upstream kinase LKB1. AMPK not only reduces the hypertrophic response, but also delays the transition from cardiac to heart failure [51]. In hypertensive patients and rats, oxidative stress and lipid peroxidation products, such as 4-hydroxy-2-nonenal (4-HNE), are elevated [52]. 4-HNE produces an inhibitory effect on the LKB1/AMPK signaling pathway, with consequent induction of mTOR/p70S6 kinase-mediated protein synthesis and cardiac myocyte cell growth. RSV prevents the pro-hypertrophic effect of 4-HNE by the activation of AMPK [53]. Thus, RSV inhibits unnecessary protein synthesis and prevents remodeling of the heart [54]. RSV has

also effects on cell proliferation. Block of cell proliferation could also improve cardiac function. In cultured rat cardiac fibroblasts, RSV inhibited their proliferation and differentiation to the hypersecretory myofibroblast phenotype; these are two critical steps in cardiac collagen deposition. Another probable mechanism through which RSV can inhibit the proliferation of cultured rat cardiac fibroblasts is the activation of the NO-cGMP signaling pathway [55]. Since inflammation is a key initiator of fibrosis, the anti-inflammatory properties of RSV could be another contributory mechanism to the changes in cardiac remodeling. In mouse cardiac fibroblasts, RSV inhibited the high expression of PI3K/Akt/ERK-dependent interleukin-17, a pro-inflammatory cytokine, induced by high glucose levels; thus, RSV may decrease high glucose-mediated myocardial inflammation and remodeling [56].

2.4. Diabetes

The term diabetes does not indicate a single pathological entity but rather a clinical syndrome characterized by chronic hyperglycemia with alterations in the metabolism of carbohydrates, fats, and proteins, due to defects in secretion and/or insulin action [57]. The cause of diabetes continues to be unknown, although researchers' attention is increasingly focused on a number of factors: the increase in obesity, the increase in the average age and life expectancy, a style of a more sedentary life, an increase in stress, and, above all, genetics. This disease is called a heterogeneous syndrome because it includes various clinical forms, of which the most frequent are type 1 or insulin-dependent diabetes mellitus (T1DM or IDDM) and type 2 or noninsulin-dependent diabetes mellitus (T2DM or NIDDM). Type 1 diabetes (also called juvenile diabetes because it occurs generally in the first 30 years of life) is determined by an autoimmune destruction of the beta cells of the Isles of Langerhans, which results in a total absence of insulin and represents about 10% of diabetes cases [58, 59]. Type 2 diabetes, which represents approximately 90% of cases, occurs predominantly after 35–40 years of age with reduced insulin secretion associated with a resistance by the tissues to the action of the hormone itself. The onset, difficult to diagnose, is characterized by hyperglycemia and consequent polyuria, polydipsia, and polyphagia. Obesity or overweight is another characteristic of individuals suffering from this pathology [60].

RSV also prevents or delays the onset of chronic age-associated diseases such as type II diabetes, improves insulin sensitivity, reduces blood glucose levels, and reduces high-fat-diet-induced obesity in rodents [56].

In a recent study, it has been reported that the multiple aspects of the action of RSV on the mechanisms control glucose homeostasis [61]. Polyphenol plays a protective role on pancreatic islets by increasing the synthesis of antioxidant enzymes, such as superoxide dismutase, glutathione peroxidase, and glutathione-s-transferase, which counteract the action of free radicals [62]. The antiapoptotic power toward β-cells has emerged both in animal models with streptozotocin toxic damage and in the autoimmune insulin of type 1 diabetes mellitus, where the action of RSV manifests itself by reducing the expression of the chemokine receptor 6 and inhibiting the migration of inflammatory cells into the pancreas [63, 64]. Furthermore, RSV modulates glycemic homeostasis at hepatic level, reducing the activity of the enzymes of gluconeogenesis and increasing, on the contrary, that of glycogen synthase [65]. At the muscle level, as well as the hepatic, the optimization of fatty acid metabolism and the reduction of

NF-kB and pro-inflammatory cytokines in the target organs are due to a direct action of the polyphenol, which induces a partial regeneration of β-cells and causes an increase in the plasma concentration of insulin [66]. In type 2 diabetes mellitus, RSV counteracts insulin resistance in rats fed with hyperlipemia diet and high in fructose as well as in those with genetically determined insulin resistance. In obese rats, in fact, the polyphenol contrasts the adipogenesis and reduces the macrophagic infiltrate in the adipose tissue, the main source of adiponectin, coresponsible for the appearance of insulin resistance [67, 68]. Furthermore, the polyphenol determines the reduction of the muscular and hepatic lipid content. These effects are due to the modulation of the action of two important intracellular regulators, a histone deacetylase (SIRT1) and an AMP-dependent kinase (AMPK), which control determinant cellular functions such as intracellular energy metabolism, mitochondrial function, and apoptosis [69]. These data have also been confirmed in primates and obese men where chronic treatment with RSV seems to improve insulin sensitivity [70]. In conclusion, the pleiotropic action of RSV makes this polyphenol a possible additional natural resource in the treatment of the diabetic patient. Its beneficial effect manifests itself through the increase of insulin secretion, the reduction of insulin resistance, and the suppression of hepatic gluconeogenesis. Furthermore, the efficacy of RSV in mitigating the autoimmune destruction of β-pancreatic cells is particularly relevant from the clinical point of view because it could represent a support to the conventional treatment of the patient with type 1 diabetes mellitus.

3. Clinical trials on resveratrol effects in cardiovascular diseases

Why resveratrol and cardiovascular diseases? From a medical standpoint, CVDs are currently the first cause of death according to WHO. So much so, that RSV has been proposed as a possible treatment for prevalent CVD in relation to all the possible cardioprotective effects that have been uprising due to its extensive research [71].

3.1. From preclinical to clinical pharmacokinetics

Most of the extensive research so far has mainly been preclinical, both in vitro and in animal models as seen before. Preclinical studies are certainly a primary fundamental approach to identifying RSV potential direct and indirect molecular targets, mechanisms, and effects. These studies, in fact, give us a preview of the possible pharmacodynamics of RSV. This, however, neglects the main obstacle of all clinical research when introducing in the human body any kind of external element, pharmacokinetics. By this, I mean absorption, distribution, metabolism, and excretion. Research so far is not abundant and is mainly done on a restricted number of individuals. Moreover, studies initially focused on total plasma and urine RSV content due to lack of suitable metabolites standards of identification and quantification. In the last years, the increased knowledge on RSV-derived metabolites in plasma and urine [72, 73], in particular trans-, cis- forms, mono- and di-glucuronides/sulfates and sulfoglucuronides, as well as dihydro-RSV (DHRSV), derived from microbiota metabolism [73, 74] has opened a new frontier on the true difference between these metabolites and their activity level [75]. Let us now take a direct view of the main human studies published on RSV pharmacokinetics:

3.2. Absorption

After oral administration, the RSV plasma peak is reached in 30–60 min. In a clinical study in healthy volunteers, the absorption after oral administration of 25 mg of RSV was 70%, the peak plasma concentration of 491 ng/ml, and the plasma half-life of 9.2 h [74]. Systemic exposure to RSV (concentration-time curve) and peak plasma concentration were decreased (by 46 and 45%, respectively) when RSV (2 g twice daily) was administered with high-fat foods [76].

Interestingly, a six-daily 4-h interval (25, 50, 100, or 150 mg) RSV intake for 13 days on 20 healthy males and 20 healthy females showed that area under curve values was not directly proportional to RSV intake, and that there is a high interindividual variability and that bio-availability was higher after morning administration [77]. Another clinical study showed that bioavailability from wine and grape juice was around six times higher than that from tablets, in 11 healthy males consequent to either a single 250 ml red wine, 10 tablets, or 1 L grape juice intake with a 0.014 mg/kg of average RSV dose. Furthermore, a similar study with 10 healthy men with single ingestion of 375 mL of red wine (6.3 mg total REA content) or 10 capsules containing grape extract (total RSV content of 4.7 mg RSV) showed that grape extract RSV absorption was delayed versus red wine and moreover remained longer in the organism yielding higher RSV-derived metabolites [73].

RSV absorption studies have been performed on animals (mouse, rat) and using human liver cells (hepatocytes) and human tumor cells (colon carcinoma). The RSV contained in red wine is mainly present in the glycosylated trans- and cis-form (The two trans and cis spatial con-formations are due to the presence of the double bond between the two phenolic rings.) The glycosidase RSV can be hydrolyzed from intestinal glucosidases to trans- and cis-RSV. In rats, it has been shown that RSV is absorbed in the intestine in a conjugated form with glucuronic acid [78].

It is estimated that in humans, 75% of the RSV administered orally is absorbed by the oral and intestinal mucosa and that the latter occurs mainly by trans-epithelial diffusion [79]. However, bioavailability is very low (<1%) and this could be due to rapid and intense metabolism and/ or by the capture of specific tissues (the liver would seem to be able to eliminate most of the RSV from the circulatory stream) [79]. The low bioavailability of RSV is associated with a low solubility in water (<1 mg/ml) [80]. Furthermore, trans-RSV is photosensitive, easily oxidized and with an unfavorable pharmacokinetic profile [81]. With daily feeding, free concentrations of RSV compatible with those that determine its biological actions in vitro (5–100 µmol) are not achieved in the target tissues nor can high doses of pure RSV be administered due to potential undesirable effects and drug interactions.

3.3. Distribution

RSV is distributed in the liver, to which it shows a high affinity, and in the kidneys and, to a lesser extent in the brain, heart, lungs, and testes (pharmacokinetic studies with C14-labeled trans-RSV) [82, 83]. RSV accumulates in conjugated, glucuronide, or sulfated forms in rat liver. Furthermore, a 12-h pharmacokinetic steady-state of RSV has been shown in a 2g RSV twice a day intake with standard breakfast and high-fat breakfast in a sample of five healthy

females and three healthy males [76]. Another interesting clinical trial on nine healthy males with single intake of 500 mL low-fat milk containing RSV (RSV dose 85.5 mg/70 kg) showed a high binding affinity of RSV glucuronide metabolites to plasma proteins [72].

3.4. Metabolism

RSV is metabolized by (1) sulfation (in the bowel/liver: limiting factor), (2) glucuronidation of the phenolic group, and (3) hydrogenation of the aliphatic double bond (intestinal microflora). Metabolic studies have shown that the most common metabolites of RSV are the derivatives conjugated with glucuronic acid (glucuronides) and sulfates, synthesized both in the liver and in the bowel. Moreover, RSV metabolism by human gut microbiota seems to have a pronounced interindividual difference as shown in a study on 12 healthy volunteers with a single oral dose of 0.5 mg RSV/kg body weight in the form of grapevine-shoot supplement [84]. In a study, in healthy volunteers treated with RSV doses of 0.5–2.5 g, the most abundant metabolite was found to be a monosulfate derivative, RSV-3-sulphate. In the blood, the concentration of RSV 3-sulfate and of the two monoglucuronide derivatives is about 20 times that of RSV; the same ratio is present when we compare the concentration-time curve (AUC) of the RSV with that of the RSV-3-sulfate (the AUC of the sulfate is about 18–23 times that of the RSV, while the AUC of the two glucuronides is 4–6 times that of RSV) [85]. Moreover, in another clinical trial, no gender or age-dependent differences were observed in RSV metabolic profile in a small sample healthy subjects distributed in six young and six elderly females and six young and six elderly males [86].

3.5. Excretion

The apparent clearance and mean volume of distribution of RSV are consistent with the low bioavailability of stilbene. The plasma half-life of RSV is between 2.9 and 8.9 h, similar to that of the two glucuronide derivatives (2.9–10.6 h) and the 3-sulfate derivative (3.2–11.5 h) [85].

4. Trying to make order on CV risk factors in human resveratrol trials

4.1. Hypertension

In the fight against cardiovascular diseases, control of arterial hypertension is what is giving the best results in terms of cost-effectiveness. The large pharmacological intervention studies have shown that the reduction of just 10% of the pressure values resulted in a 40% reduction in mortality from cerebrovascular accidents and 16–20% in mortality from coronary accidents. However, criteria must be followed to set up a rational and adequate treatment to bring the values of blood pressure back to norm or as close as possible to the norm. The first criterion must be based on the degree of hypertension, mild, moderate, or severe which, even if it has a purely indicative value, appears to be extremely useful on the clinical-therapeutic level. In fact, in the patient with mild hypertension, a sufficiently protracted period of controlled clinical observation, up to 4–5 months, is necessary before starting a therapy, since the pressure

could fall within the normal values either spontaneously or with simple hygienic-dietetic measures. Moreover, in mild hypertension, it is advisable to start with a "light" drug therapy, in monotherapy, since the blood pressure control is often easy and the risk of complications is projected far in time and is, however, low. In case of moderate or severe hypertension, on the other hand, there is no longer any doubt as to the appropriateness of immediate pharmacological treatment. In this case, the patient will be initiated to the therapy that must be undertaken gradually and continuously, besides a "step-up," a "step-down" or a "side-step" therapeutical approach. Another criterion used for the purposes of the therapeutic approach is that which is based on the presence or absence of an organ damage, i.e., on the consequences of hypertension. It is evident that the treatment of hypertension that has already caused heart failure, cerebrovascular accidents, or renal failure possesses much more difficult problems than hypertension without obvious complications and requires a considerable commitment on the part of the doctor. A third criterion is that of the presence of concomitant pathologies on which some antihypertensive drugs can negatively interfere or whose treatment can negatively interact with that of hypertension. Fortunately, the vast majority of cases of hypertension are represented as already mentioned by the mild and uncomplicated form so the problem of how to set up the therapy is not so crucial and basically identifies with the problem of choosing the drug or drugs more suitable. The choice of antihypertensive drug is, in fact, still today substantially empirical. In fact, we do not have criteria that allow us to make rational therapeutic choices, that is to say, based on the physiopathological characteristics of the hypertensive state. At most, we can rely on some clinical data, which have some connection with the pathophysiology, but which are not strictly physiopathological. In this hypertension overview, it is important to understand where RSVs place lays. On a pure clinical logical standpoint, RSV could be of great use in two main occasions: first, in borderline hypertension in which drugs have shown to have a degree of adverse effects and so we have this time span in which we, as of today, have no other treatment if not a dietary one and second, it could be a great ally in all degrees of hypertension in association with the standard FDA recommended drugs.

Let us see, however, if this perspective view is backed by clinical trial evidence.

As already specified before, clinical trials today are not sufficient to give a definite all-around answer, but the evidence today at hand is comforting. In fact, a randomized, crossover, double-blind, single-dose, placebo-uncontrolled clinical trial with a single ingestion of 30, 90, 270 mg of synthetic RSV or placebo at weekly intervals, with analyses performed 1 h after consumption on nine healthy over-weighted/obese men or postmenopausal women with mildly elevated blood pressure, showed an acute RSV effect on FMD, which improved by 65% after consumption of 30 or 90 mg RSV and by 88% with 270 mg [87]. Another double-blind, randomized, placebo-controlled, crossover clinical trial on 18 patients with 330 mg of grape seeds and skin, 100 mg of green tea, 60 mg of RSV, 60 mg blend of quercetin and ginkgo biloba and bilberry on a 28 day basis showed a significant reduction in diastolic blood pressure [88]. RSV's main purpose has been studied by this clinical crossover, randomized, double-blind, placebo-controlled, single-center trial, which confirmed that RSV for 4 weeks lowers BP in prehypertensive and stage 1-hypertensive patients [89]. Another interesting study justifies the idea of RSV acting in cohort with standard drugs; in fact, monitoring BP in patients with hypertension (BP prior to and following standard antihypertensive treatment plus RSV,

compared with a control group receiving standard antihypertensive treatment alone) showed that diastolic BP and systolic BP were significantly reduced with the addition of RSV to standard therapy [90] (**Table 1**). Despite great hopes, these studies are still insufficient for RSV recommendation in hypertension as more and better-performed trials must be done in terms of higher sample size and longer follow-ups, without forgetting the pharmacokinetic issue.

4.2. Atherosclerosis

Although atherosclerosis is a slowly progressive disease, at the same time it can be extremely dangerous, considering the risk of its evolution in heart attacks and strokes. Prevention is the best cure: we have seen that obesity is one of the predisposing factors for atherosclerosis; therefore, it is recommended to follow a low-calorie diet, to reduce weight and to practice constant exercise. For the same reason, patients suffering from atherosclerosis or otherwise at risk should stop smoking; hypertensives should constantly monitor blood pressure values to avoid very high peaks, which, as analyzed, can predispose the subject to atherosclerosis and its complications. For similar discourse for patients with high cholesterol, it is recommended to undergo regular blood tests and follow a low-fat diet of lipids, to ensure the body a fair level of cholesterol in the blood. All these risk factors have in common the increased inflammatory state and lipid levels, which lead to mechanical and metabolic damage of the endothelial cells and deposit of lipidic and fibrotic matrix.

According to this, it is clear that an intervention on risk factors and behavioral habits can often block the cascade of events that would inevitably lead to the formation of atheroma.

Sample population	Dose	Duration	Effects	Reference
Hypertension				
19 healthy over-weighted/obese men or postmenopausal women with mildly elevated blood pressure	30, 90, 270 mg of synthetic RSV or placebo at weekly intervals or placebo	Analyses performed 1 h after consumption	FMD improved by 65% after consumption of 30 or 90 mg RSV and by 88% with 270 mg	[87]
18 patients	330 mg of grape seed and skin, 100 mg of green tea, 60 mg of RSV, 60 mg of blend of quercetin and ginkgo biloba and bilberry or placebo	28 days	Significant reduction in diastolic blood pressure	[88]
50 participants with prehypertension and 50 participants with stage 1 hypertension	500 mg of capsules, twice daily or placebo	4 weeks treatment–4 weeks washout–4 weeks treatment	Reduction in blood pressure	[89]
46 stage I hypertension and 51, stage II hypertension patients	Evelor or placebo	6 months	Diastolic BP and systolic BP were significantly reduced with the addition of RSV to the standard therapy	[90]

Table 1. Summary of clinical effects of resveratrol in hypertension.

Atherosclerosis is now a treatable disease: compliance with certain behavioral rules, prevention of risk factors and, possibly, the administration of specific drugs can not only block the degeneration of the disease but also and above all favor its regression.

In this sense, it is interesting to highlight the few clinical trials that invest in RSV and its role on atherosclerosis and on its two main components: oxidative stress and lipid profile.

A randomized, placebo-controlled 40 mg RSV capsule daily for 6 weeks on 20 healthy adults showed that RSV's cellular activity has a direct influence on plasma biomarkers associated with inflammation and risk of various diseases, in terms of reduction in reactive oxygen species generation, p47 and intranuclear nuclear factor-kappaB binding, jun-N-terminal kinase-1, inhibitor of kappaB-kinase-beta, phosphor-tyrosine phosphatase-1B expression, and cytokine signaling-3 suppression in mononuclear cells when compared with the baseline and the placebo. PCE intake also suppressed plasma concentrations of TNF-alpha, IL-6, and C-reactive protein [91]. On the same false line, a crossover, placebo-controlled trial with a high-fat high-carbohydrate meal with placebo or 100 mg of RSV and 75 mg of grape skin polyphenol on a small sample of four healthy male and six healthy women showed an increase in Nrf-2 binding activity following the meal and increased mRNA expression of NQO-1 and GST-π1 genes and attenuated postprandial rise in CD14 and IL-1β mRNA and TLR4 protein in mononuclear cells, and a decreased plasma endotoxin concentration, thus demonstrating an acute reduction in postprandial inflammatory state [92]. A more straightforward study on the possible use of RSV in primary lone prevention of atherosclerosis done on a sample of 44 healthy subjects in a 1 month time period with a double-blind, randomized, placebo-controlled administration of 400 mg of trans-RSV, 400 mg of grape skin extract, and 100 mg of quercetin showed a decreased expression of endothelial cell ICAM, VCAM, and IL-8 as well as a decreased level of plasma IFN-γ and insulin [93]. Other two straightforward studies instead tried to study the possible use of RSV in combination with standard atherosclerosis treatment. In the first, 75 patients on statins treatment at high CVD risk on a three-parallel arm, randomized, triple-blind, placebo-controlled trial on a 6-month daily ingestion of 350 mg placebo (n = 25), RSV containing grape extract (GE-RSV, grape phenolics +8 mg RSV, n = 25) or conventional grape extract lacking RSV (GE) showed a decrease in ApoB (−9.8%) and LDLox (−20%) in RSV-treated patients, beyond their treatment according to standard guidelines for primary prevention of CVD. In the second, with the same cohort as the first but on a 12-month daily ingestion of 350 mg placebo (n = 25), RSV containing grape extract (GE-RSV, grape phenolics +8 mg RSV, n = 25) or conventional grape extract lacking RSV (GE) for 6 months and the double dose for the following 6 months showed a GE-RSV nutraceutical decreased hsCRP (−26%), TNF (−19.8%), PAI-1 (−16.8%), and IL-6/IL-10 ratio (−24%), and increased IL-10 (19.8%). Furthermore, both studies showed no drug interactions or adverse effects [94, 95].

Worth mentioning is a study on healthy smokers, as we said before, smoking is not only an atherosclerosis risk factor but an overall CVD risk factor. In particular, randomized, double-blind, crossover trial on 50 healthy adult smokers, which were allocated to either "RSV-first" group (30 days of 500 mg RSV/day, 30 days washout, 30-day placebo) or to "placebo-first" group (30-day placebo, 30 days washout, 30 days of 500 mg RSV/day) showed a significant CRP and triglyceride concentrations reduction and increased total antioxidant status values [96] (**Table 2**).

Sample population	Dose	Duration	Effects	Reference
Atherosclerosis				
20 healthy adults	40 mg of RSV capsule daily or placebo	6 weeks	Reduction in reactive oxygen species generation, p47 and intranuclear nuclear factor-kappaB binding, jun-N-terminal kinase-1, inhibitor of kappaB-kinase-beta, phosphor-tyrosine phosphatase-1B expression, and cytokine signaling-3 suppression in mononuclear cells when compared with the baseline and the placebo	[91]
Four healthy male and six healthy women	100 mg of RSV and 75 mg of grape skin polyphenol or placebo	1, 3, and 5 hours after meal intake	Acute reduction in postprandial inflammatory state	[92]
44 healthy subjects	400 mg of trans-RSV, 400 mg of grape skin extract and 100 mg of quercetin or placebo	1 month	Decreased expression of endothelial cell ICAM, VCAM and IL-8 as well as a decreased level of plasma IFN-γ and insulin	[93]
75 patients on statins treatment at high CVD risk	RSV-containing grape extract (GE-RSV, grape phenolics +8 mg RSV) or conventional grape extract lacking RSV (GE) or placebo	6 months	Decrease in ApoB (−9.8%) and LDLox (−20%) in RSV-treated patients	[94]
75 patients on statins treatment at high CVD risk	RSV-containing grape extract (GE-RSV, grape phenolics +8 mg RSV) or conventional grape extract lacking RSV (GE) or placebo	6 months + double dose for the following 6 months	Decreased hsCRP (−26%), TNF (−19.8%), PAI-1 (−16.8%) and IL-6/IL-10 ratio (−24%), and increased IL-10 (19.8%)	[95]
50 healthy adult smokers	500 mg of RSV/day or placebo	30 days of 500 mg RSV/day (or placebo), 30 days washout, 30-days of 500 mg RSV/day (or placebo)	Significant CRP and triglyceride concentrations reduction, and increased total antioxidant status values	[96]

Table 2. Summary of clinical effects of resveratrol in atherosclerosis.

These trials took together, although still insufficient as evidence, give us a broad perspective on RSV use in atherosclerosis. RSV supplementation due to its anti-inflammatory, antioxidant, and hypotriglyceridemic effects, it is beneficial to those with increased CVD risk factors, both high and low, such as smokers and as a lone primary prevention therapy as well as in association therapy. Even if repetitive, more and better-performed trials must be done in terms of higher sample size and longer follow-ups in order to recommend RSV as an atherosclerosis therapy.

4.3. Heart diseases

Heart disease is the leading cause of death for men and women of all racial groups and affects all population ages, thus representing the leading cause of death in industrialized countries. Among these, coronary artery disease (CAD) is the most common condition associated with high mortality and morbidity. Clinical manifestations of ischemic heart disease include silent ischemia, stable and unstable angina pectoris, myocardial infarction (MI), heart failure, and sudden death. It has been widely ascertained that acute coronary syndromes in their various forms of presentation share a common pathophysiological mechanism, such as the rupture or erosion of the atherosclerotic plaque (of which we have already mentioned the uses of the RSV), on which phenomena overlap thrombotic and embolism at the distal level, as well as pro-inflammatory state and endothelial dysfunction.

In these terms, we understand the importance of preventing diseases which once again, for the umpteenth time, can only be done by prevention of heart disease that expresses the only winning weapon. Depending on the general health of the patient, it may be necessary to administer drugs for the heart, for obesity, for hypertension, and for hypercholesterolemia, as well as to follow a healthy and balanced diet, without excess exercise constantly. In this context, we try to understand through the various trials available to us how the administration of RSV can also act on the heart component directly without forgetting the already-mentioned beneficial effects associated.

In 40 stable CAD patients, a randomized, two-parallel arm, double-blind, placebo-controlled trial with a 3-month daily ingestion of 10 mg RSV in one of the groups showed that RSV decreased, versus baseline, LDL (8%) and improved endothelial function (50%), left ventricular diastolic function (2%), and protected from unfavorable hemorheologic changes. This highlights the RSV's cardioprotective effects after myocardial infarction [97]. Another interesting trial in 116 patients with stable angina pectoris in a randomized, double-blind, active-controlled, and parallel trial with three groups of subjects who received the test drugs and one control group of subjects who were not randomized with inclusion, 30 and 60 days of oral supplementation with calcium fructoborate (CF) (112 mg/day), RSV (20 mg/day), and their combination showed a significant hs-CRP decrease in all groups at the 30- and 60-day visits: 39.7% at 60 days for the CF group and 30.3% RSV plus CF at 60 days. The N-terminal prohormone of BNP was significantly lowered by RSV (59.7% at 60 days) and by CF (52.6% at 60 days). However, their combination was the most effective and induced a decrease of 65.5%. Lipid markers showed slight changes from baseline in all groups. Overall, this study confirmed the anti-inflammatory and lipid effect of RSV and introduces RSVs effect on left ventricle function enhancement, or more correctly recover, as shown by N-BNP marker [98]. Last but not the least, in 75 patients with stable CAD in a three-parallel arm, randomized, triple-blind, dose-response, placebo-controlled trial with a 12-month daily ingestion of 350 mg placebo (n = 25), RSV-containing grape extract (GE-RSV, grape phenolics +8 mg RSV, n = 25) or conventional grape extract lacking RSV (GE) for 6 months and the double dose for the following 6 months showed a significant increase in adiponectin levels (10%) in GE-RSV

group in addition to a decrease in PAI-1 levels, non-HDL cholesterol decreased significantly in both GE and GE-RSV groups, and downregulation of pro-inflammatory genes expression in PBMCs isolated from GE-RSV group patients. This highlights RSV's possible fibrinolytic effect on such patients confirming its overall anti-inflammatory effect in patients with established disease as did the two trials before [75].

Looking at these three trials and their results, the main suggestion would be to use RSV as an enhancement to the therapies now at our disposal for patients with previous cardiovascular accidents as it has shown not only to be of great importance for prevention of heart diseases through its anti-inflammatory and lipid profile effects but it also seems as it can modify left ventricle function (**Table 3**). Of course, three trials are away from sufficient to make such suggestion an indication, as so much has still to be done.

4.4. Diabetes type 2

Diabetes care is a very complex and articulated. The therapeutic objective is the same for any type of diabetes and consists in taking down high levels of blood glucose within the normal blood glucose values. This objective is more than anything else from a real need since hyperglycemia

Sample population	Dose	Duration	Effects	Reference
Heart diseases				
40 stable CAD patients	Daily ingestion of 10 mg RSV or placebo	3 months	Decreased LDL (8%) and improved endothelial function (50%), left ventricular diastolic function (2%) and protected from unfavorable hemorheologic changes versus baseline	[97]
116 patients with stable angina pectoris	Calcium fructoborate (CF) (112 mg/day), RSV (20 mg/day), and their combination or placebo	30 and 60 days	Significant hs-CRP decrease in all groups at the 30-day and 60-day visits: 39.7% at 60 days for the CF group and 30.3% at 60 days for RSV plus CF. The N-terminal prohormone of BNP was significantly lowered by RSV (59.7% at 60 days) and by CF (52.6% at 60 days). However, their combination was the most effective and induced a decrease of 65.5%. Lipid markers showed slight changes from baseline in all groups. Overall, this study confirmed the anti-inflammatory and lipid effect of RSV and introduces RSVs effect on left ventricle function enhancement, or more correctly recover, as shown by N-BNP marker	[98]
75 patients with stable CAD	RSV-containing grape extract (GE-RSV, grape phenolics +8 mg RSV) or conventional grape extract lacking RSV (GE) or placebo	6 months + double dose for the following 6 months	Increase in adiponectin levels (10%) in GE-RSV group in addition to a decrease in PAI-1 levels, non-HDL cholesterol decreased significantly in both GE and GE-RSV groups and downregulation of pro-inflammatory genes expression in PBMCs isolated from GE-RSV group patients	[75]

Table 3. Summary of clinical effects of resveratrol in heart diseases.

depends not only on the symptoms but also on acute and long-term complications of diabetes mellitus. Therefore, treatments that allow the achievement of the aforementioned objective deserve a quote: the adoption of a healthy and balanced diet, the regular practice of exercise and the intake of specific drugs for the reduction of blood sugar. Finally, concluding this rapid overview of diabetes therapy, it is important to note the importance of the regular monitoring of the effectiveness of the treatments adopted. This aspect is important because it allows the attending physician to understand if the therapy in place is working or not.

In this view, RSV can play an important role, let us see the understandings of few trials at our disposal. In 19 type 2 diabetics, a two-parallel arm, randomized, double-blind, placebo-controlled trial with a daily ingestion of 10 mg RSV for 4 weeks (n = 10 or placebo, n = 9) showed a decrease in insulin resistance possibly due to a decrease in oxidative stress and improvement of insulin signaling via the Akt pathway [99]. In another study, 62 type 2 diabetics in a randomized, two- parallel arm, placebo uncontrolled, unblinded trial with a 3-month daily ingestion of hypoglycemic drugs +250 mg RSV (n = 28) or only hypoglyce-mic drugs in control group (n = 29) showed that RSV improved systolic and diastolic blood pressures, HbA1c (−5%), total cholesterol, and LDLc concentrations [100]. On the same line, another interesting study on 66 type 2 diabetics in a randomized placebo-controlled, double-blind, parallel clinical trial supplemented with 1 g/day of RSV for 45 days showed significant decrease in systolic blood pressure, fasting blood glucose, hemoglobin A1c, insulin, and insulin resistance, while HDL was significantly increased, when compared to their baseline levels [101].

These studies considered as a whole show that RSV has many important antidiabetic effects as it improves insulin sensitivity, glycemic control, and also acts on associated risk factors such as inflammation and lipid profile (**Table 4**). Overall, RSV seems to have all the main specifics for the perfect antidiabetic drug. Although, as expected, more trials are needed since the observed reductions in HbA1c and HDL with RSV supplementation are so signifi-cant, compared to the benefits achieved with frontline antidiabetic drugs; we can hope for the best.

Sample population	Dose	Duration	Effects	Reference
Type 2 diabetes				
19 type 2 diabetics	Daily ingestion of 10 mg of RSV or placebo	4 weeks	Decrease in insulin resistance possibly due to a decrease in oxidative stress and improvement of insulin signaling via the Akt pathway	[99]
62 type 2 diabetics	Hypoglycemic drugs +250 mg RSV(or placebo)	3 months	Improved systolic and diastolic blood pressures, HbA1c (−5%), total cholesterol, and LDLc concentrations	[100]
66 type 2 diabetics	1 g/day of RSV or placebo	45 days	Decrease in systolic blood pressure, fasting blood glucose, hemoglobin A1c, insulin, and insulin resistance, while HDL was significantly increased, when compared to their baseline levels	[101]

Table 4. Summary of clinical effects of resveratrol in type 2 diabetes.

5. Effects of resveratrol in cerebrovascular diseases

The most frequent cause of death in the western world, after heart disease and cancer, is cerebrovascular disease and is the second most common cause of neurological disability, after Alzheimer's disease [102]. It has been found that half of the patients with neurological diseases also present cerebrovascular diseases. The term cerebrovascular disease indicates any cerebral alteration resulting from a pathological process affecting the blood vessels, whether they are arteries, arterioles, capillaries, veins, or venous sinuses (venous sinus). The vascular lesion may have anatomopathological characteristics of an occlusion by a thrombus or an embolus, or a rupture; the consequences at the level of the cerebral parenchyma are of two types: ischemia (with or without infarction) and hemorrhage. An alteration of the vessel wall permeability, hypertension, and increase in blood viscosity or modifications of another rheological characteristic are other pathophysiological mechanisms involved in cerebrovascular pathology.

The most common presentations of cerebrovascular diseases are stroke and transient ischemic attack (TIA). Stroke is caused by cerebral ischemia, that is the interrup-tion of the blood flow to the brain, of the duration enough to determine the appearance of focal signs and symptoms that do not disappear within 24 h, while, TIA consists in a sudden appearance of focal signs and symptoms, attributable to transient cerebral ischemia, which disappear within 24 h.

Most cerebrovascular diseases depend on atherosclerosis and arterial hypertension, and the main forms are characterized by cerebral insufficiency caused by transient disturbances of the blood flow. Moreover, diseases such as diabetes and atherosclerosis can be complicated by hypertension and increase the viscosity of the blood, without forgetting the important role of aging. In fact, an altered vascular permeability is responsible for headache, cerebral edema, and seizures of hypertensive encephalopathy. Signs and symptoms of cerebrovascular diseases reflect the damaged brain areas and not necessarily the affected artery.

The main causes are the formation of atherosclerotic plaques at the level of the carotids, embolisms from the heart, hematological disorders, fibromuscular dysplasia, and vasculitis, i.e., inflammatory processes in the blood vessels that cause the lumen to shrink [102].

5.1. Resveratrol in cerebrovascular diseases

Neurodegenerative diseases share common features such as chronic vascular damage due to oxidative stress and inflammation damage, which underline neural damage and thus neuronal death. Taking into account the mechanisms associated with vascular damage, let us see the role of RSV. As already mentioned, RSV has been shown through great preclinical evidence to have strong anti-inflammatory properties, as well as many antioxidant capacities, apoptosis inhibition, multiple transcriptional signaling pathways, and direct neurological function. As many works show, RSV inflammatory-response inhibition in the nervous system is mainly due to a reduction in TNFα, iNOS, COX-2, IL-1α, IL-1β, MMP-9, and p-p53, all inflammatory markers of great neural importance [103]. Reduction in oxidative stress is mainly mediated by an increase in eNOS, NO, SOD, GPx1, CAT, HO-1 levels accompanied by a decrease in MPO and ROS. Other important oxidative stress mechanisms include an increase in GSH,

VEGF, Trx-2, and mitochondrial biogenesis, while a reduction in XO and MDA. RSV apoptosis inhibition function is associated with a reduction in caspase-3, caspase-7, CYT-c, and Bax with increased Bcl-2. Finally, RSV's direct neuroprotective properties can be identified in the reduction of neurological deficit score and β-amyloid peptide with a contemporary increase in neuron survival, motor function and in TH, dopamine, and AchE levels. Main signaling pathways, protein kinase, and transcriptional factor modulators include Nrf-2, NFκB, p38MAPK, PGC-1 h, PI3K/Akt, mTOR, PPAR, AMPK, CREB, PKC, and SIRT [104–109].

5.2. Clinical trials on resveratrol effects in cerebrovascular diseases

Although RSV's neurological properties are many, the study of the pathologies of the nervous system is still very complex due to the missing knowledge in the exact mechanisms, so we can only depend on biomarkers of the single pathologies.

As far cerebrovascular diseases are considered, two are the main works at our disposal. The first work, on 4 young healthy men and 20 women in a double-blind, placebo-controlled, crossover with a single or once daily on 3 separate days with 250 or 500 mg of RSV, showed that RSV increased cerebral blood flow and hemoglobin but did not enhance cognitive function. Interestingly, the blood flow increase was dose dependent [110]. The second work evaluated if RSV use in coadministration with r-tPA for brain ischemic stroke treatment is more effective than r-tPA alone. These 312 patients were randomly divided according to their onset-to-treatment time (OTT) (early OTT or delayed OTT); afterward they were either treated with the association of r-tPA and placebo or with r-tPA plus RSV. Patients receiving delayed OTT r-tPA plus RSV treatment showed a reduction in matrix metalloproteinase (MMP)-2 and MMP-9 plasma levels; moreover, reductions in both MMPs and patient NIHSS scores were observed [111].

These two trials show a positive effect of RSV in cerebrovascular diseases both in a possible chronic use as seen by the increase in the cerebral blood flow and in an acute state for its positive effects in coadministration with r-tPA. Overall, it is almost impossible to evaluate RSV use in specific cerebrovascular diseases; as of now its use in stroke is the only plausible prospective indication. Of course, the way is still long and both preclinical and clinical trials are needed.

As far as neurodegenerative disease go, at our disposal, there are only two clinical trials both on Alzheimer disease (AD). These two studies were conducted on similar cohorts of 119 patients in a randomized, placebo-controlled, double-blind, multisiter, phase 2 trial manner. In both, 500 mg was administered once daily, with 500 mg dose escalation every 13 weeks, ending with 1000 mg of administration twice daily for 12 months, which, however, found different understandings. The first study showed a reduced CSF MMP9, increased IL-4, and attenuated decline in Aβ42 and Aβ40, while the second showed the same attenuation in Aβ42 and Aβ40 accompanied by increased brain volume loss [112, 113] (**Table 5**).

Overall, these two studies are useful to conclude that RSV metabolites penetrate the blood-brain barrier and have effects on the central nervous system, and these effects are mainly associated with an anti-inflammatory and antineurodegenerative effect. Collectively, we could assess that there is a place for RSV in neurodegenerative disease treatment; however, we are

Sample population	Dose	Duration	Effects	Reference
Cerebrovascular diseases				
Four young healthy men and 20 women	Single or once daily on three separate days 250 or 500 mg of RSV or placebo	After a 45-min resting absorption period	Increased cerebral blood flow and hemoglobin but did not enhance cognitive function	[110]
312 brain ischemic stroke patients	r-tPA + placebo or with r-tPA + resveratrol	24 hours after the treatment, outcomes were assessed	Reduction in matrix metalloproteinase (MMP)-2 and MMP-9 plasma levels; moreover, reductions in both MMPs and patient NIHSS scores were observed	[111]
119 patients	500 mg once daily, with 500 mg dose escalation every 13 weeks, ending with 1000 mg twice daily administration	12 months	Reduced CSF MMP9, increased IL-4, and attenuated decline in Aβ42 and Aβ40	[112]
119 patients	500 mg once daily, with 500 mg dose escalation every 13 weeks, ending with 1000 mg twice daily administration	12 months	Attenuation in Aβ42 and Aβ40 accompanied by increased brain volume loss	[113]

Table 5. Summary of clinical effects of resveratrol in cerebrovascular diseases.

still to understand which viable targets RSV focuses on which could be the biomarkers useful to understand RSV activity and effectiveness. As for as cerebrovascular disease considered, here as well, much is to be done in both preclinical and clinical stages.

6. Conclusion

Prevention policies mainly invest in medical interventions, although it has been known for several years, that lifestyle changes, mainly focused on exercise and nutrition, can produce a significant reduction in cardiovascular risk, with antiatherosclerotic effects, antithrombotic, anti-ischemic, antiarrhythmic with a significant reduction in mortality and incidence of infarction. Dietary and physical activity changes, together with the improvement of body composition, give a sense of general well-being. On the contrary, pharmacological interventions, together with their indispensable curative effect, unfortunately almost always present side effects that worsen the quality of life.

The presented data in this study have demonstrated the role of resveratrol in prevention of cardiovascular abnormalities induced by atherogenic diet. The overall data revealed that resveratrol possesses the cardioprotective effect by improving the serum lipid profile, antioxidant system, improving lipid metabolism, and cardiac tissue damages either in myocardium and aorta.

On the basis of the beneficial properties that resveratrol evoked on human health, the findings support a role for regular consumption of dietary resveratrol by consumption of resveratrol-rich fruits or vegetables to avoid the risk of cardio- and cerebrovascular diseases, in order to add life to the years and not only years to life.

Acronyms and abbreviations

AMPK	adenosine monophosphate-activated protein kinase
Bax	Bcl-2-associated X protein
Bcl-2	B-cell lymphoma 2
CAT	catalase
COX	cyclooxygenase
CREB	cAMP response element binding
Cyt-c	cytochrome C
eNOS	endothelial nitric oxide synthase
GPx	glutathione peroxidase
GSH	glutathione
HO-1	heme oxygenase-1
IL	interleukin
iNOS	inducible nitric oxide synthase
MAPKs	mitogen-activated protein kinases
MDA	malondialdehyde
MMP	matrix metallopeptidase
MPO	myeloperoxidase
mTOR	mammalian target of rapamycin
NF-κB	nuclear factor kappa B
NO	nitric oxide
Nrf	nuclear factor-E2-related factor
p53	tumor protein 53
PGC	peroxisome proliferator-activated receptor-gamma coactivator
PI3K	phosphoinositide 3-kinase

PKC	protein kinase C
PPAR	peroxisome proliferator-activated receptor
ROS	reactive oxygen species
RSV	resveratrolo
SIRT1	sirtuin 1
SOD	superoxide dismutase
TH	tyrosine hydroxylase
TNFα	tumor necrosis factor alpha
Trx	thioredoxin
VEGF	vascular endothelial growth factor
XO	xanthine oxidase

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