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A Systematic Review on Natural Antioxidant Properties of Resveratrol

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Polyphenols, including anthocyanins, flavonoids and stilbenes, which constitute one of the most abundant and ubiquitous groups of plant metabolites, are an integral part of the human diet. Resveratrol (3,5,4'-trihydroxystilbene), a naturally occurring polyphenol produced by some plants as a self-defence agent, has an antifungal activity. Resveratrol has been found in some plants (such as grapevine, pine and peanuts) and is considered to have beneficial effects also on human health. The number of studies on resveratrol greatly increased in PubMed database since 1997, after the anticancer effect of this molecule was first reported. The interest in resveratrol in grape was originally sparked by epidemiological studies indicating an inverse relationship between long-standing moderate consumption of red wine and the risk of coronary heart disease; this effect has been ascribed to resveratrol, which possesses diverse biochemical and physiological properties, including antiplatelet and anti-inflammatory proprieties, and provides a wide range of health benefits ranging from chemoprevention to cardioprotection. Recently, resveratrol has been described as an anti-aging compound. The consumption of resveratrol (red wine) together with a Mediterranean diet or a fast-food meal ("McDonald'sMeal") had a positive impact on oxidized (ox-) LDL and on the expression of oxidative and inflammatory genes. Therefore, this review summarized the most important scientific data about healing and preventive potential of resveratrol, acting as cardioprotective, neuroprotective, chemopreventive and antioxidant agent.

Keywords: Red wine, Health, Liver disease, Cardiovascular disease, Cancer chemoprevention, Anti-aging, Neuro-protective, Mediterranean diet.

Phytoalexin molecules are of enormous chemical diversity, but those from the *Vitaceae*, *Fabaceae* and *Pinaceae* seem to constitute a somewhat restricted group belonging to the stilbene family of compounds, consisting of two aromatic rings joined by a methylene bridge. The skeleton of stilbenes is based on the resveratrol molecule (3,5,4'-trihydroxystilbene) in *Vitaceae* and *Fabaceae* or pinosylvin (*trans*-3,5-dihydroxystilbene) in *Pinaceae*. Resveratrol (Figure 1), produced by several plant species, is found in two isoforms: *trans*-resveratrol and *cis*-resveratrol. The trans isomer, which possesses a greater biological activity due to the presence of the 4'-hydroxystyryl group, was first detected in 1940 in the roots of white hellebore (*Veratrum grandiflorum*) [1].The content and distribution of resveratrol in plants has attracted growing attention in recent years, particularly with the respect to fruit and vegetables commonly eaten by humans, due to its dual implications in plant protection and human health.

Resveratrol has been found in at least 72 plant species distributed among 31 genera and 12 families. All of the families, found to contain resveratrol, belong to the spermatophytes division: *Vitaceae*, *Myrtaceae*, *Dipterocarpaceae*, *Cyperaceae*, *Gnetaceae*, *Fabaceae*, *Pinaceae*, *Moraceae*, *Fagaceae*, *Liliaceae* [2, 3]. On the other hand, the compound has been reported in few fruit and vegetable products included in the human diet (grapes, wine, grape juice, cranberries, peanuts). In 2003, resveratrol was found in hops, and suggested that this molecule could also be found in beer [4]; instead in 2006, Counet *et al*. [5] found *trans*-resveratrol and *trans*-piceid in dark chocolate and cocoa liquor, although the antioxidant

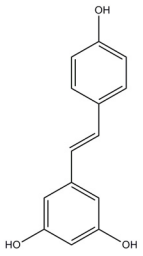

Figure 1: Structure of resveratrol.

activity of chocolate is probably related to its high procyanidin content rather than the presence of stilbenes (0.4 mg/kg *trans*-resveratrol and 1 mg/kg *trans*-piceid, the glucoside of resveratrol, in dark chocolate and 0.5 mg/kg *trans*-resveratrol and 1.2 mg/kg *trans*-piceid in cocoa liquor) [5].

Resveratrol and related stilbenes in plants are strongly implicated as an important mechanism in host defence against infection and injury, being synthesized as response to biotic and abiotic stress, such as fungal infection [6], ultra violet light exposure [7, 8], ozone stress [9], anoxic treatment [10], and wounding [6]. This molecule is derived from the acetate-malonate and phenylpropanoid pathways of primary and secondary metabolism of the plant, respectively. The condensation of *p*-coumaroyl CoA with three molecules of malonyl CoA is accomplished through stilbene synthase activity. Four moles of CO_2 are released for each mole of resveratrol synthesised. Resveratrol synthesis in grape is then catalysed by the stilbene

synthase (STS) enzyme, which utilizes *p*-coumaryl-CoA and malonyl CoA as the substrate. The same substrates are also utilized by chalcone synthase (CHS) for the production of chalcone, the precursor of flavonoids. Chalcone synthase indeed catalyses a reaction involving one *p*-coumaroyl CoA and three malonyl CoA molecules, but in this instance only three CO_2 molecules are generated. The product is naringenin chalcone which, in a further series of reactions, gives rise to the flavonoid family. Two gene families for CHS and STS have been identified in *Vitis vinifera*, one of the plant species in which the markedly high amounts of resveratrol are naturally found. Grapevine genome sequencing reported in 2007 revealed a marked expansion of STS genes (43 genes identified in addition to the 20 previously identified), suggesting the great importance of stilbene metabolism for this species [11]. Several plants have been genetically modified by transferring the STS gene to produce *trans*-resveratrol in order to investigate its potential roles in health promotion in humans and disease control in plants, such as tobacco, tomato and poplar [12-14]. Products from grapes, the world's second largest fruit crop, are considered as the most important available human dietary source of resveratrol. Grape germplasm resources are being able to provide abundant quantities of natural resveratrol products. Therefore, it is of utmost importance to accurately measure the resveratrol content in grape germplasm in order to utilize germplasm resources to produce resveratrol and/or in breeding programs, to obtain new cultivar berries containing high quantities of resveratrol.

Stilbene synthesis takes place in the skin and seeds of berries [15-17], but has also been detected in the stem, axillary bud, shoot tip, petiole, root and leaf of grapevine, at constitutive levels ranging from 0.2 mg/kg FW to 16.5 mg/kg FW. Stem phloem tissue contains the greatest amounts of resveratrol, whereas leaves have the lowest.

In grapevine and interspecific varieties, the resveratrol content of UV irradiated grape berries decreased proportionately from the green stage to complete maturity, being close to zero in ripe fruit. The geographical area in which grapes are cultivated appears to influence the level of resveratrol in wine; overall, the red varieties had a higher content than the white/pink ones. The highest total resveratrol content was found in varieties such as Pinot Noir and Pinot Tete de Negre (>20 mg/kg of FW of total grape berry), and the lowest in Teroldego and Rebo (<1 mg/kg of FW of total grape berry).

Romero-Pèrez *et al*. [18] measured the level of resveratrol in 36 grape juices and found that the average concentration in red samples is ten-fold higher than that in the white juices. The great variability was also observed: the total resveratrol content ranged from 0.69 to 14.47 mg/l in red samples and 0 to 1.44 mg/l in white samples. As found by Li *et al*. 2006 [17] in grape berries, the fresh juices from the wine-making grape varieties had more total resveratrol content than the commercial juices. Thus, grape juice, in particular red grape juice, may be an alternative dietary source to wine to achieve the beneficial effects of resveratrol [18, 19].

Moreover, the efficacy of dietary resveratrol may be greater when included in the diet rather than taken in the form of a compound in pills. It has been suggested that the presence of quercetin, which interfere with resveratrol removal, might diminish the catabolism of the phytoalexin, and therefore increase its levels in serum [20, 21]. Also, there are indications that the combination of resveratrol and quercetin could enhance the effects of these compounds on triacylglycerol metabolism. However, further studies are required to verify this. Resveratrol is poor soluble in water and the preparation of proper formulation with satisfactory bioavailability of this molecule present a real challenge [22]. For many years, the benefits of fruits and vegetables have long been considered due to their fibers, minerals and vitamin contents, but studies made in the last few decades have highlighted the importance of phytochemicals in preventing disease and increasing life expectancy.

An ever-increasing number of persons are becoming aware of the importance of the healthy diet, and the challenges that it incurs. The life expectancy of humans can be prolonged by an appropriate diet, rich in vegetables and fruit, which contain antioxidants; of course, a correct diet cannot be considered as panacea, since genetic factors also play a significant role in life expectancy. Yet, foodstuffs with a relevant antioxidant effects contain molecules that can prevent damage to the cellular system incurred by oxygen radicals O2 (ROS). The diet that has been inversely related to the mortality from cardiovascular diseases [23] contains a wide range of predominantly phenolic bioactive compounds, including flavonols (*e.g*. myricetin and kaempferol, quercitin, catechin and epicatechin, proanthocyanidins, anthocyanins, phenolic acids and stilbene resveratrol). Thousands of articles that describe the metabolism and bioactive proprieties of resveratrol and its close derivatives, were published in the last 20 years. In particular, the increasing interest shown in resveratrol is due to the discovery of its numerous biological activities and its beneficial effect on human health, providing protection from heart disease, cancer neuron damage, skin conditions and the effects of aging [20, 24-38].

The interest in this molecule in grape was originally sparked by epidemiological studies indicating an inverse relationship between moderate consumption of red wine over a long period of time and risk of coronary heart disease. This discovery, made in the early nineties, gave rise to the term "French Paradox": even if a positive correlation between a high saturated fat intake and high mortality from coronary heart disease (CHD) has been found worldwide, in France, where red wine is consumed generally in moderate quantities, it was not confirmed [28]. This biological attribute ascribed to resveratrol has been borne out by a large body of evidence demonstrating resveratrol's pharmacological activities.

Resveratrol provides protection against cardiovascular diseases [39] (CVD), currently the leading cause of death, and a relevant health problem worldwide. Some of the major risk factors for CVD, such as age, sex, genetic predisposition, diet, and lifestyle are constant. Moreover, it is widely accepted that excessive dietary intake of saturated fats and cholesterol play a role in the onset and development of CVD through changes in plasma low-density lipoprotein-cholesterol (LDL-c) [40, 41]. However, non-lipid risk factors can also contribute to the development of CVD. About one half of the deaths due to this condition occur in individuals with normal cholesterol levels [40, 42]. It is believed that risk factors other than raised plasma cholesterol may play an important role in the development of CVD [43]. Novel pharmaceutical and dietary strategies, so-called "functional foods", provide a new window of opportunity in the efforts being made to reduce CVD.

At the concentration obtainable physiologically by the consumption of red wine, resveratrol increases the expression of endothelial nitric oxide (NO) synthase in human vascular endothelial cells, which is responsible for synthesizing the potent vasodilator, nitric oxide [44]; it also decreases the expression of the potent vasoconstrictor, endothelin [44]. Other mechanisms underlying the cardio-protective effects of resveratrol include the inhibition of platelet aggregation, similar to aspirin, and its antioxidant effects on cholesterol metabolism [39].

Resveratrol has an important effect on endothelial cells injury. It maintains a balance between vasodilators, such as NO, and vasoconstrictors, such as endothelin-1 (ET-1) [45] which, together, provide thrombus-resistance, and prevent atherogenesis [46]. Recent studies have shown that resveratrol has the ability to regulate the production of these important compounds [47]. Normally, when endothelial injury occurs, platelets adhere to the subendothelial matrix of a damaged vessel, spread over its surface and recruit additional platelets to form a thrombus. Improper regulation or over reactivity of this repair system can lead to the thrombosis. Findings reported in several *in vitro* and *in vivo* studies showed that platelet aggregation by a number of agonists is suppressed by resveratrol [31, 48, 49]. As reported by Wang *et al*. in 2002 [31], the administration of resveratrol (4 mg/kg/day) to rabbits with a high cholesterol diet caused a 35% reduction in the average ADP-induced platelet aggregation rate (PAR) in compare with the animals given a standard diet.

Resveratrol has been found to significantly inhibit LDL oxidation [26, 33, 49], which is the key event in the initiation of endothelial injury and the induction of pro-inflammatory molecules expression in endothelial cells. High plasma LDL levels are associated with an increased risk of atherosclerosis [50], and in numerous studies it has been found that resveratrol protects lipids from peroxidative degradation and inhibits the uptake of oxidized LDLs in the vascular wall [51, 52].

Vascular dysfunction is the initial step in the onset of many cardiovascular system diseases states concurrent with diabetes [53]. Oxidative stress is the key mechanism in the pathogenesis of diabetes-related vascular dysfunction, and the inactivation of nitric oxide by ROS is known be a crucial factor in reducing NO bioavailability and the development of endothelial dysfunction [54]. NAD(P)H oxidase is a key source of superoxide (O_2^-) in the vasculature [55]. Previous studies demonstrated that Tumor Necrosis Factor-*alpha* (TNF-α) treatment inhibits NAD(P)H oxidase activation in coronary arterioles from mice with type 2 diabetes [56]. TNF-α is reported to down-regulate NOS expression in the fat and muscle of obese rodents [57]. Several studies have also reported that resveratrol attenuates TNF-α expression activated by lipopolysaccharides (LPS) [58, 59], suggesting that resveratrol protects the organism against vascular dysfunction in diabetics by attenuating TNF-α induced vascular oxidative stress [60]. Furthermore, it has been shown that resveratrol induces major cellular anti-oxidant enzymes (e.g. glutathione peroxidase, heme oxygenase, superoxide dismutase) in cardio-vascular cells [61], thus leading to a marked attenuation in oxidative stress. Resveratrol downregulates both the vascular and cardiac expression of TNF-α and inhibits NADPH oxidases in the vasculature [60, 62, 63]. Importantly, resveratrol inhibits the mitochondrial production of ROS in the vasculature [40]. For the first time Di Renzo *et al*. [64, 65] observed the effect of resveratrol (in red wine), in association with McDonald's and a Mediterranean meal, on ox-LDL and gene expression. When red wine is associated with the two types of meals, values of ox-LDL are lowered and expression of antioxidant genes is increased, while chemokine C-C motif ligand 5 (CCL5) expression is decreased. CCL5, a chemotactic cytokine plays diverse roles in the pathology of inflammatory disease [64, 65].

Recently, Kantartzis *et al*. [66] studied the effects of 12-week resveratrol supplementation on liver fat content and cardiometabolic risk parameters in overweight, obese and insulin-resistant volunteers. No effects of resveratrol supplementation on cardiometabolic risk parameters were observed. However, it is worth of noting that the variability in liver fat content was very large and tissue biopsy was not performed. Therefore, some resveratrol effects on molecular level might have not been recorded.

It was also observed that resveratrol could slow down the effects of aging. The socio-economic and health implications of increased human life expectancy are related to an increase in the healthcare burden incurred by age-related diseases. Anti-aging pharmacological treatment should thus increase the quality of life by decreasing the risk of age-associated diseases [67-69].

One of the most widely proposed strategies designed to reduce the effects of age is dietary restriction [70] defined as a reduction in nutrient intake in the absence of malnutrition [71]. Thus, experimental studies have demonstrated that dietary reduction increases lifespan in a variety of different experimental organisms, including yeast, nematodes, flies and rodents [71, 72]. Dietary restriction increases the lifespan as well as the period of life spent in relatively good health and free of age-associated disease [73]. A particular class of enzymes, called sirtuins, seems to mediate some of the effects of dietary restriction [74]. There are seven members of the sirtuin class of enzymes in mammals – SIRT-1 to SIRT-7 [20]. Sirtuins regulates a number of intracellular pathways via the activation of transcription factors and enzymes responsive to nutrient availability. SIRT-1, the major sirtuin activated through both calorie restriction and resveratrol, mediates the beneficial impact of each on longevity and health [75]. SIRT-1 acts by deacetylating transcription factors, such as the tumor suppressor p53, the FOXO family of transcription factors FOXO1, FOXO3 and FOXO4 and the transcription factors NF-kB [76-78]. The importance of the FOXO transcription factor in the mammalian aging process, recently revealed in reports from three independent studies, suggests that there is an association between an increase in longevity and FOXO 3A gene [79, 80]. Moreover, as is well known, NF-kB is the master regulator of the immune/inflammatory response; by regulating NF-kB, SIRT-1 may inhibit the expression of genes involved in inflammation that is directly related with the NF-kB signaling pathway [81, 82]. SIRT-1 is involved in other vital processes, such as DNA repair, cell survival, gluconeogenesis, muscle cell differentiation, cell cycle regulation lipid metabolism fat mobilization and sensitivity to insulin [83]. The physiological actions of SIRT-1 are mediated in part of their ability to deacetylase nucleosomal histone proteins at specific residues for histone H4 lysine 16 [84, 85]. It has been suggested that a potential cause of aging is failure to control the structure of chromatin which, once SIRT-1 is activated, mediates intracellular responses by regulating non-histone cellular substrates [20, 86]. Therefore, it has been suggested that resveratrol mimics the protective effects of dietary restriction, since it can activate the mammalian sirtuin in SIRT-1 *in vitro* assays [87]. However, it is widely debated whether resveratrol is a direct activator of SIRT-1 [88]. Resveratrol may not lead to the direct activation of SIRT-1 with p53 native peptide substrate [89] although a convincing body of evidence both *in vivo* and *ex vivo* showed that resveratrol and its metabolites can promote a SIRT 1-dependent cellular response, as demonstrated by resveratrol-induced decreases in acetylation of various known SIRT-1 targets [90]. In addition, the over expression of SIRT-1 in endothelial cells can mimic many of the effects of resveratrol, whereas SIRT-1 depletion tends to attenuate the resveratrol-induced cellular effect [30, 91-93]. The ability of resveratrol to mimic lower energy intake was originally tested in two parallel experiments in mice [94, 95]. When mice were on high fat diet, resveratrol restored their normal lifespan by preventing conditions leading to early death, but it also improved insulin sensitivity and motor function [90, 94]. In mice on a normal diet, resveratrol did not increase lifespan significantly [94], although its possible effects at higher doses have not been

investigated. Moreover, dietary restriction may reduce mitochondria-derived ROS production, in accordance with the mitochondrial theory of species. Therefore, mitochondria-derived ROS might accelerate the aging process in pathological conditions, such as diabetes and the metabolic syndrome [74]; in addition, an increasing number of studies now suggest that resveratrol plays an important role in protecting mitochondria and attenuating mitochondrial ROS production. Many experiments confirmed that resveratrol reverses hyperglycaemic status in high fat-induced obese rodents and animal models with type 1 diabetes. It was observed that the oral administration of resveratrol at dose of 22.4 mg/kg/day improves insulin sensitivity and slightly reduces body weight in one-year-old mice on a high fat diet. At a dose of 400 mg/kg/day, resveratrol prevents diet-induced obesity and alleviates obesity-related insulin resistance; in the diabetic rat, it has been shown that resveratrol decreases plasma glucose and lipid levels in a dependent fashion [90, 94, 96]. However, Zhang *et al*. [60] demonstrated that resveratrol neither alters body weight nor reduces hyperinsulinemic hyperglycaemia in $Lepr^{db}$ mice (an animal model in which a genetic modification incurs a defect in receptor for the obese gene product, leptin). Zhang *et al*. [60] suggest that resveratrol has therapeutic effects, especially on vascular complications, which can also occur independently of weight loss and hyperglycaemic status. It is well-established that age-associated low-grade inflammation accelerates the incidence of coronary artery disease and stroke in the elderly. The consequences of increased oxidative stress in aging include functional inactivation of NO by high concentrations of O_2^-, resulting in significant vasomotor dysfunction [30], increased apoptosis of endothelial cells [97, 98], and impaired mitochondrial biogenesis [91, 92, 99]. Recent studies provide clear evidence that resveratrol treatment can also confer vasoprotection in aged mice and rats, thus attenuating ROS production, improving endothelial function, inhibiting inflammatory processes and decreasing the rate of endothelial apoptosis [29, 95]. Further studies of this type are required in order to clarify whether resveratrol might be used as a drug in humans to prevent vascular injury and its fatal complications.

There has been a focus on the involvement of resveratrol in neuron protection against neurodegenerative diseases. The study by Virgil and Contestabile [100], which appeared in 2000 was the first to suggest a neuroprotective property of resveratrol against excitotoxic brain injury: the authors compared the effect of systemic administration of an excitotoxin kainic acid (KA) in young adult rats, and found that chronic resveratrol treatment prior to KA administration considerably reduced the damages caused by KA in the olfactory cortex and the hippocampus. Multiple cell culture investigations and *in vivo* studies in animal models of neurodegenerative diseases/brain injury show that resveratrol is a potent neuroprotective compound. Interesting neuroprotective effects are probably mediated through multiple mechanisms that may include the inhibition of the: voltage-gated potassium current [101], electrical activity of CA1 neurons [102] and/or excitatory synaptic glutamate receptors [101]. In cell culture studies, resveratrol treatments reduced the effects of many types of brain injury, such as ethanol induced neuronal cell death [103, 104] in the presence of amyloid *beta*-peptide, a neurotoxic peptide believed to play a role in the pathogenesis of Alzheimer's disease [105, 106], and the loss of dopaminergic neurons in rat primary midbrain neuron-glial cultures treated with lipopolysaccharides (LPS) via anti-inflammatory activity [107]. In 2011, Liu *et al*. demonstrated in rat model of spinal cord injury that resveratrol treatment provides neuroprotection and functional recovery via its anti-oxidant, anti-apoptotic and anti-inflammatory actions [108]. Resveratrol treatment was also found to provide neuroprotection in animal models of Huntington's disease via the activation of *Ras* extra-cellular signal regulated kinase [109], and in a rat model of multiple sclerosis probably via anti-inflammatory activity [103, 110].

Also, some preclinical studies provoke resveratrol supplementation in promoting cognition. Based on the new meta-analysis of randomized controlled trials, although resveratrol enhances some cognitive performance measures outcomes were inconsistent probably due to the different dose (75 - 500 mg), the length of the trial period, heterogeneity of the participants [111]. Numerous studies are in progress with the aim to gain a better understanding of the association/correlation between the human nervous system and resveratrol.

Moreover, the valuable data are obtained concerning the safety and tolerability of resveratrol in humans [112], while its clinical pharmacokinetic and metabolism profiles have now been defined yet. So far, 16 studies on resveratrol are available in literature, and another six, which have been completed, are forthcoming; they include trials that investigate the potential role of resveratrol in the management of type 2 diabetes, Alzheimer's disease, and cancer [113]. However, in only a small number of clinical trials resveratrol was used as a single-agent and its safety and tolerability was investigated [62, 114-117].

Resveratrol also plays a key chemopreventive role against cancer; epidemiological studies suggests that a higher flavonoid intake is associated with lower cancer risk [118], the molecule affecting all three stages of carcinogenesis (initiation, promotion, and progression) by modulating the signal transduction pathways controlling cell division and growth, apoptosis, inflammation, angiogenesis, and metastasis, and is therefore considered as a promising anticancer agent by some authors [119]. The anticancer property of resveratrol has been supported by findings indicating that it inhibits the proliferation of a wide variety of human tumour cells *in vitro*. These data have prompted numerous preclinical studies designed to evaluate the potential of resveratrol in cancer chemoprevention and chemotherapy [118-123]. In the first study on the anticancer property of resveratrol in literature, an experiment was conducted on skin cancer development in mice treated with a carcinogen. Indeed chemoprevention, the prevention of cancer by the ingestion of chemical agents that reduce the risk of carcinogenesis, is one of the most direct ways of reducing its morbidity and mortality. Cancer chemopreventive agents include nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin, aspirin, piroxicam, and sulindac (inhibitors of cyclooxygenase, COX) [124]. Resveratrol was identified as a potent inhibitor of COX [125], and therefore a potent chemopreventive agent against cancer. So, there are many metabolic pathways by which resveratrol can take a determinant role. One of the most important ways of the prevention of the development of cancer is by the induction of apoptosis, which may be mediated by either death receptors or signals arising from within the cell (i.e. via a mitochondrial mechanism) or by the generation of reactive oxygen species [123]. The induction of apoptosis selectivity in cancer cells is regarded as an important strategy for cancer prevention as well as therapy. Resveratrol has been reported to induce apoptosis in various cancerous or transformed cells in culture, chemically induced mouse skin tumours and in transplanted tumours in nude mice by activating both the extrinsic and intrinsic pathways of cell death mechanisms [126-128]. Resveratrol induces apoptosis by activating pro-apoptotic signalling molecules as well as inhibiting the anti-apoptotic molecules of the intracellular signalling molecules of the intracellular signal transduction pathways [128]. Resveratrol also seems to have the power to inhibit angiogenesis by

disrupting angiogenesis signalling cascades, a process that is believed to be the frontline of attack by various anti-cancer agents. Findings of paramount importance in the literature, confirm the anti-angiogenetic effects of resveratrol. Increased metabolic activity and oxygen consumption by rapidly proliferating cells make solid tumours more likely to maintain an intratumoral hypoxic environment [129, 130], which promotes tumour cell adaptation by inducing hypoxia responsive genes [131, 132]. The data collected by several laboratories show that resveratrol exerts its anti-proliferative effect by targeting members of the apoptotic family in cancer of various tissues, such as the prostate, breast, brain, endometrium, blood rectum, pancreas, skin, lung, ovary and bladder [133,134].

Chemotherapy is often used as the front-line regimen in the treatment of most cancer types. However, the development of tumour resistance to chemotherapy, so called chemoresistance, is a major hurdle in cancer therapy [135, 136]. Chemosensitization is an effective tool in overcoming chemoresistance, whose mechanisms in tumours can be intrinsic (cells resistant before treatment) or acquired (resistance develops during treatment) [132]. These mechanisms may depend on, for example, drug influx and efflux, inactivation of chemotherapeutic agents, alterations in target molecules, enhanced DNA repair, growth factor signalling, and/or alterations in cell-death regulation. Resveratrol exerts its sensitization effect by modulating one or more mechanisms of resistance. Findings in most of the recent reports in the literature indicate that resveratrol sensitizes tumour cells to chemotherapeutic agents by modulating cell survival proteins; for example, to sensitize human cancer cell lines to chemotherapeutic agents such as doxorubicin cytarabine (AraC), actinomycin D, taxol, and methotrexate by down-regulating any surviving expression and increasing apoptosis [135, 137, 138]. Likewise, in another study, resveratrol-potentiated apoptosis was found to be induced by chemotherapeutic agents such as a cisplatin, gefitinb, and paclitaxed in multidrug-resistance non-small-cell lung cancer cells, the process being associated with a decrease in surviving expression [135]. Furthermore, studies on the pharmacokinetics of resveratrol in humans have concluded that even high doses of resveratrol might be insufficient to achieve the resveratrol concentration required *in vivo* for the systemic prevention of cancer [115, 118]. This observation is consistent with the findings made in animal cancer models, which indicate that the *in vivo* effectiveness of resveratrol is limited by its poor systemic bioavailability [33, 139, 140]. The most convincing evidence of the anticancer effect of resveratrol has been obtained in tumours where direct contact with the molecule was enabled (such as cancer of the skin and gastrointestinal tract). For other cancers, the evidence is uncertain, even if massive doses of resveratrol are used [118, 139].

Additional proof of the wide potential of resveratrol presents the recent investigation of resveratrol as possible agent in the treatment of infertility. It was observed that resveratrol supports the growth of follicles in the culture model derived based on donated human ovarian tissue [141].

According to all, many pre-clinical studies provided promising evidences about different resveratrol benefits. As natural and biologically active compound the consumption of resveratrol is generally recognized as well-tolerated and safe. However, the outcomes of clinical studies are inconsistent and limited. Regarding the poor bioavailability of the most of the commercially available resveratrol supplements, the application of improved oral dosage forms is necessary. Therefore, more clinical studies on resveratrol as single agent, which will measure wide range of parameters, are needed in order to determine conclusively the effect of resveratrol on the human health.

References

[1] Takaoka M. (**1940**) Phenolic substances of white hellebore (*Veratrum grandiflorum* Loes. fil.). II. Synthesis of resveratrol and its derivatives. *Proceedings of the Imperial Academy (Tokyo)*, ***16***, 405-407.

[2] Langcake P, Pryce RJ. (**1976**) The production of resveratrol by *Vitis vinifera* and other members of the Vitaceae as a response to infection or injury. *Physiological Plant Pathology*, ***9***, 77−86.

[3] Takaya Y, Yan K-X, Terashima K, He Y-H, Niwa M. (**2002**) Biogenic reactions on stilbene tetramers from Vitaceaeous plants. *Tetrahedron*, ***58***, 9265–9271.

[4] Callemien D, Counet C, Cawet Q, Collin S. (**2003**) Hop as a determinant nutrition key for health. Proceedings of the 29th European brewery convention congress, Fachverlag Hans Karl, Germany. 1375–1382.

[5] Counet C, Callemien D, Collin S. (**2006**) Chocolate and cocoa: New sources of *trans*-resveratrol and *trans*-piceid. *Food Chemistry*, ***98***, 649-657.

[6] Chung IM, Park MR, Chun JC, Yun SJ. (**2003**) Resveratrol accumulation and resveratrol synthase gene expression in response to abiotic stresses and hormones in peanut plants. *Plant Science*, ***164***, 103–109.

[7] Adrian M, Jeandet P, Douillet-Breuil AC, Tesson L, Bessis R. (**2000**) Stilbene content of mature *Vitis vinefera* berries in response to UV-C elicitation. *Journal of Agricultural and Food Chemistry,* ***48***, 6103–6105.

[8] Versari A, Parpinello GP, Tornielli GB, Ferrarini R, Giulivo C. (**2001**) Stilbene compounds and stilbene synthase expression during ripening, wilting, and UV treatment in grape cv. Corvina. *Journal of Agricultural and Food Chemistry,* ***49***, 5531-5536.

[9] Grimmig B, Gonzalez-Perez MN, Welzl G, Penuelas J, Schubert R, Hain R, Heidenreich B, Betz C, Langebartels C, Ernst D, Sandermann Jr. H. (**2002**) Ethylene- and ozone-induced regulation of a grapevine resveratrol synthase gene: different responsive promoter regions. *Plant Physiology and Biochemistry*, ***40***, 865–870.

[10] Jiménez B, Orea JM, Ureña AG, Escribano P, López de la Osa P, Guadarrama A. (**2007**) Short anoxic treatments to enhance *trans*-resveratrol content in grapes and wine. *European Food Research and Technology*, ***224***, 373–378.

[11] Jaillon O, Aury JM, Noel B, Policriti A, Clepet C, Casagrande A, Choisne N, Aubourg S, Vitulo N, Jubin C, Vezzi A, Legeai F, Hugueney P, Dasilva C, Horner D, Mica E, Jublot D, Poulain J, Bruyère C, Billault A, Segurens B, Gouyvenoux M, Ugarte E, Cattonaro F, Anthouard V, Vico V, Del Fabbro C, Alaux M, Di Gaspero G, Dumas V, Felice N, Paillard S, Juman I, Moroldo M, Scalabrin S, Canaguier A, Le Clainche I, Malacrida G, Durand E, Pesole G, Laucou V, Chatelet P, Merdinoglu D, Delledonne M, Pezzotti M, Lecharny A, Scarpelli C, Artiguenave F, Pè ME, Valle G, Morgante M, Caboche M, Adam-Blondon AF, Weissenbach J, Quétier F, Wincker P. (**2007**) The grapevine genome sequence suggests ancestral hexaploidization in major angiosperm phyla. *Nature*, ***449***, 463–467.

[12] Giorcelli A, Sparvoli F, Mattivi F, Tava A, Balestrazzi A, Vrhovsek U, Calligari P, Bollini R, Confalonieri M. (**2004**) Expression of the stilbene synthase (StSy) gene from grapevine in transgenic white poplar results in high accumulation of the antioxidant resveratrol glucosides. *Transgenic Research*, ***13***, 203–214.

[13] Halls C, Yu O. (**2008**) Potential for metabolic engineering of resveratrol biosynthesis. *Trends in Biotechnology*, ***26***, 77–81.

[14] Delaunois B, Cordelier S, Conreux A, Clément C, Jeandet P. (**2009**) Molecular engineering of resveratrol in plants. *Plant Biotechnology Journal*, ***7***, 2–12.

[15] Creasy LL, Coffee M. (**1988**) Phytoalexin production potential of grape berries. *Journal of the American Society for Horticultural Science*, ***113***, 230-234.

[16] Jeandet P, Bessis R, Gautheron B. (**1991**) The production of resveratrol (3,5,4′-trihydroxystilbene) by grape berries in different developmental stages. *American Journal of Enology and Viticulture*, ***42***, 41-46.

[17] Li X, Wu B, Wang L, Li S. (**2006**) Extractable amounts of *trans*-resveratrol in seed and berry skin in Vitis evaluated at the germplasm level. *Journal of Agricultural and Food Chemistry*, ***54***, 8804–8811.

[18] Romero-Pérez AI, Ibern-Gómez M, Lamuela-Raventós RM, de La Torre-Boronat MC. (**1999**) Piceid, the major resveratrol derivative in grape juices. *Journal of Agricultural and Food Chemistry*, ***47***, 1533–1536.

[19] Colica C, De Lorenzo A, Abenavoli L. (**2018**) Mediterranean diet in liver steatosis: the role of polyphenols. *Minerva Gastroenterologica e Dietologica*, ***64***, 97-99.

[20] Baur JA, Sinclair DA. (**2006**) Therapeutic potential of resveratrol: the *in vivo* evidence. *Nature Reviews Drug Discovery*, ***5***, 493-506.

[21] Borriello A, Cucciolla V, Della Ragione F, Galletti P. (**2010**) Dietary polyphenols: Focus on resveratrol, a promising agent in the prevention of cardiovascular diseases and control of glucose homeostasis. *Nutrition, Metabolism & Cardiovascular Diseases*, ***20***, 618-625.

[22] Guerrero RF, García-Parrilla MC, Puertas B, Cantos-Villar E. (**2009**) Wine, Resveratrol and Health: a Review. *Natural Product Communication*s, ***4***, 635-658.

[23] Grønbeak M. (**2002**) Alcohol, type of alcohol and all-cause and coronary heart disease mortality. *Annals of the New York Academy of Sciences, **957***, 16-20.

[24] Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CW, Fong HH, Farnsworth NR, Kinghorn AD, Mehta RG, Moon RC, Pezzuto JM. (**1997**) Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science*, ***275***, 218-220.

[25] Athar M, Back JH, Tang X, Kim KH, Kopelovich L, Bickers DR, Kim AL. (**2007**) Resveratrol: A review of preclinical studies for human cancer prevention. *Toxicology and Applied Pharmacology*, ***224***, 274-283.

[26] Belguendouz L, Fremont L, Linard A. (**1997**) Resveratrol inhibits metal ion-dependent and independent peroxidation of porcine low-density lipoproteins. *Biochemical Pharmacology*, ***53***, 1347-1355.

[27] Niles RM, Cook CP, Meadows GG, Fu YM, McLaughlin JL, Rankin GO. (**2006**) Resveratrol is rapidly metabolized in athymic (nu/nu) mice and does not inhibit human melanoma xenograft tumor growth. *Journal of Nutrition*, ***136***, 2542-2546.

[28] Renaud S, De Lorgeril M. (**1992**) Wine, alcohol, platelets and the French Paradox for coronary heart disease. *Lancet*, ***339***, 1523-1529.

[29] Ungvari Z, Orosz Z, Labinskyy N, Rivera A, Xiangmin Z, Smith K, Csiszar A. (**2007**) Increased mitochondrial H_2O_2 production promotes endothelial NF-κB activation in aged rat arteries. *American Journal of Physiology-Heart and Circulatory Physiology*, ***293***, H37-H47.

[30] Ungvari Z, Labinskyy N, Mukhopadhyay P, Pinto JT, Bagi Z, Ballabh P, Zhang C, Pacher P, Csiszar A. (**2009**) Resveratrol attenuates mitochondrial oxidative stress in coronary arterial endothelial cells. *American Journal of Physiology-Heart and Circulatory Physiology*, ***297***, H1876-H1881.

[31] Wang Z, Huang Y, Zou J, Cao K, Xu Y, Wu JM. (**2002**) Effects of red wine and wine polyphenol resveratrol on platelet aggregation *in vivo* and *in vitro*. *International Journal of Molecular Medicine*, ***9***, 77-79.

[32] Wenzel E, Soldo T, Erbersdobler H, Somoza V. (**2005**) Bioactivity and metabolism of *trans*-resveratrol orally administrated to Wistar rats. *Molecular Nutrition & Food Research*, ***49***, 482-494.

[33] Zou JG, Huang YZ, Chen Q, Wei EH, Hsieh TC, Wu JM. (**1999**) Resveratrol inhibits copper ion-induced and azo compound-initiated oxidative modification of human low density lipoprotein. *Biochemistry and Molecular Biology International*, ***47***, 1089-1096.

[34] Chillemi R, Sciuto S, Spatafora C, Tringali C. (**2007**) Anti-tumor properties of stilbene-based resveratrol analogues: Recent results. *Natural Product Communications*, ***2***, 499-513.

[35] Spatafora C, Basini G, Baioni L, Grasselli F, Sofia A, Tringali C. (**2009**) Antiangiogenic resveratrol analogues by mild *m*-cpba aromatic hydroxylation of 3,5-dimethoxystilbenes. *Natural Product Communications*, ***4***, 239-246.

[36] Dias K, Nikolaou S. (**2011**) Does the combination of resveratrol with Al (III) and Zn (II) improve its antioxidant activity? *Natural Product Communications*, ***6***, 1673-1676.

[37] Mozafari M, Nekooeian AA, Mashghoolozekr E, Panjeshahin MR. (**2015**) The cardioprotective effects of resveratrol in rats with simultaneous type 2 diabetes and renal hypertension. *Natural Product Communications*, ***10***, 335-338.

[38] Laneri S, Sacchi A, Fratter A, Bertin W, Bino A, Vertuani S, Manfredini S. (**2017**) Self-nanoemulsifying system in the accumulation of resveratrol and N-acetylcysteine in the epidermis and dermis. *Natural Product Communications*, ***12***, 1785-1787.

[39] Markus MA, Morris BJ. (**2008**) Resveratrol in prevention and treatment of common clinical conditions of aging. *Clinical Interventions in Aging*, ***3***, 331-339.

[40] Das M, Das DK. (**2010**) Resveratrol and cardiovascular health. *Molecular aspects of Medicine*, ***31***, 503-512.

[41] Murray CJ, Lopez AD. (**1997**) Global mortality, disability, and the contribution of risk factors: global burden of disease study. *Lancet*, ***349***, 1436-1442.

[42] Castelli WP. (**1998**) The new pathophysiology of coronary artery disease. *American Journal of Cardiology*, ***82***, 60T-65T.

[43] Abeywardena MY. (**2003**) Dietary fats, carbohydrates and vascular disease: Sri Lankan perspective. *Atherosclerosis*, ***171***, 157-161.

[44] Nicholson SK, Tucker GA, Brameld JM. (**2008**) Effects of dietary polyphenols on gene expression in human vascular endothelial cells. *The Proceedings of the Nutrition Society*, ***67***, 42-47.

[45] Kinlay S, Libby P, Ganz P. (**2001**) Endothelial function and coronary artery disease. *Current Opinion in Lipidology*, ***12***, 383-389.

[46] Davingnon J, Ganz P. (**2004**) Role of endothelial dysfunction in atherosclerosis. *Circulation*, ***109***, III27-III32.

[47] Rubbo H, Trostchansky A, Botti H, Batthyány C. (**2002**) Interaction of nitric oxide and peroxynitrite with low-density lipoprotein. *Biological Chemistry*, ***383***, 547-552.

[48] Lin KH, Hsiao G, Shih CM, Chou DS, Sheu JR. (**2009**) Mechanisms of resveratrol-induced platelet apoptosis. *Cardiovascular Research*, ***83***, 575-585.

[49] Wu JM, Hsieh TC. (**2011**) Resveratrol: a cardioprotective substance. *Annals of the New York Academy of Sciences*, ***1215***, 16-21.

[50] Dichtl W, Nilsson L, Goncalves I, Ares MP, Banfi C, Calara F, Hamsten A, Eriksson P, Nilsson J. (**1999**) Very low-density lipoprotein activates nuclear factor-*kappa*B in endothelial cells. *Circulation Research*, ***84***, 1085-1094.

[51] Abenavoli L, Milic N, Luzza F, Boccuto L, De Lorenzo A. (**2017**) Polyphenols treatment in patients with nonalcoholic fatty liver disease. *Journal of Translation Internal Medicine*, ***5***, 144-147.

[52] Leighton F, Cuevas A, Guasch V, Pérez DD, Strobel P, San Martín A, Urzua U, Díez MS, Foncea R, Castillo O, Mizón C, Espinoza MA, Urquiaga I, Rozowski J, Maiz A, Germain A. (**1999**) Plasma polyphenol and antioxidants, oxidative DNA damage and endothelial function in diet and wine intervention study in humans. *Drugs Under Experimental and Clinical Research*, ***25***, 133-141.

[53] Blann AD, Lip GY. (**1998**) The endothelium in atherothrombotic disease: assessment of function, mechanisms and clinical implications. *Blood Coagulation & Fibrinolysis*, ***9***, 297-306.

[54] Shah AM, Channon KM. (**2004**) Free radicals and redox signalling in cardiovascular disease. *Heart*, ***90***, 486-487.

[55] Griendling KK. (**2006)** NADPH oxidases: new regulators of old functions. *Antioxidant Redox Signal*, ***8***, 1443-1445.

[56] Gao X, Belmadani S, Picchi A, Xu X, Potter BJ, Tewari-Singh N, Capobianco S, Chilian WM, Zhang C. (**2007**) Tumor necrosis factor-*alpha* induces endothelial dysfunction in Lepr(db) mice. *Circulation*, ***115***, 245-254.

[57] Valerio A, Cardile A, Cozzi V, Bracale R, Tedesco L, Pisconti A, Palomba L, Cantoni O, Clementi E, Moncada S, Carruba MO, Nisoli E. (**2006**) TNF-*alph*a downregulates eNOS expression and mitochondrial biogenesis in fat and muscle of obese rodents. *Journal of Clinical Investigation*, ***116***, 2791-2798.

[58] Ma ZH, Ma QY, Sha HC, Wang LC. (**2006**) Effect of resveratrol on lipopolysaccharide-induced activation of rat peritoneal macrophages. *Nan fang yi ke da xue xue bao*, ***26***, 1363-1365.

[59] Marier JF, Chen K, Prince P, Scott G, del Castillo JR, Vachon P. (**2005**) Production of *ex vivo* lipopolysaccharide-induced tumor necrosis factor-*alpha*, interleukin-1*beta*, interleukin-6 is suppressed by *trans*-resveratrol in a concentration-dependent manner. *Canadian Journal of Veterinary Research*, ***69***, 151-154.

[60] Zhang H, Zhang J, Ungvari Z, Zhang C. (**2009**) Resveratrol improves endothelial function: role of TNF-α and vascular oxidative stress. *Arteriosclerosis, Thrombosis, and Vascular Biology*, ***29***, 1164-1171. 2009.

[61] Ungvari Z, Orosz Z, Rivera A, Labinskyy N, Xiangmin Z, Olson S, Podlutsky A, Csiszar A. (**2007**) Resveratrol increases vascular oxidative stress resistance. *American Journal of Physiology-Heart and Circulatory Physiology*, ***292***, H2417-H2424.

[62] Chow HH, Garland LL, Hsu CH, Vining DR, Chew WM, Miller JA, Perloff M, Crowell JA, Alberts DS. (**2010**) Resveratrol modulates drug- and carcinogen-metabolizing enzymes in a healthy volunteer study. *Cancer Prevention Research*, ***3***, 1168-1175.

[63] Zhang H, Morgan B, Potter BJ, Ma L, Dellsperger KC, Ungvari Z, Zhang C. (**2010**) Resveratrol improves left ventricular diastolic relaxation in type 2 diabetes by inhibiting oxidative/nitrative stress. *American Journal of Physiology-Heart and Circulatory Physiology*, ***299***, H985-H994.

[64] Di Renzo L, Carraro A, Valente R, Iacopino L, Colica C, De Lorenzo A. (**2014**) Intake of red wine in different meals modulates oxidized LDL level, oxidative and inflammatory gene expression in healthy people: a randomized crossover trial. *Oxidative Medicine and Cellular Longevity, **2014**,* 1-9.

[65] Di Renzo L, Marsella LT, Carraro A, Valente R, Gualtieri P, Gratteri S, Tomasi D, Gaiotti F, De Lorenzo A. (**2015**) Changes in LDL oxidative status and oxidative and inflammatory gene expression after red wine intake in healthy people: a randomized trial. *Mediators of Inflammation*, ***2015***, 1-13.

[66] Kantartzis K, Fritsche L, Bombrich M, Machann J, Schick F, Staiger H, Kunz I, Schoop R, Lehn-Stefan A, Heni M, Peter A, Fritsche A, Häring HU, Stefan N. (**2018**) Effects of resveratrol supplementation on liver fat content in overweight and insulin-resistant subjects: A randomized, double-blind, placebo-controlled clinical trial. *Diabetes, Obesity and Metabolism*, ***20***, 1793-1797.

[67] Hadley EC, Lakatta EG, Morrison-Bogorad M, Warner HR, Hodes RJ. (**2005**) The future of aging therapies. *Cell*, ***120***, 557-567.

[68] Sinclair DA, Guarente L. (**2006**) Unlocking the secrets of longevity genes. *Scientific American*, ***294***, 48-57.

[69] Pallàs M, Junyent F, Verdaguer E, Beas-Zarate C, Camins A. (**2010**) Aging control with resveratrol. *Drug Discovery today: therapeutic Strategies*, ***7***, 51-56.

[70] Ingram DK, Zhu M, Mamczarz J, Zou S, Lane MA, Roth GS, deCabo R. (**2006**) Calorie restriction mimetics: an emerging research field. *Aging Cell*, ***5***, 97-108.

[71] Lin SJ, Kaeberlein M, Andalis AA, Sturtz LA, Defossez PA, Culotta VC, Fink GR, Guarente L. (**2002**) Calorie restriction extends Saccharomyces cerevisiae lifespan by increasing respiration. *Nature*, ***418***, 344-348.

[72] Cantó C, Auwerx J. (**2009**) Caloric restriction, SIRT 1 and longevity. *Trends in Endocrinology and Metabolism*, ***20***, 325-331.

[73] Colman RJ, Anderson RM, Johnson SC, Kastman EK, Kosmatka KJ, Beasley TM, Allison DB, Cruzen C, Simmons HA, Kemnitz JW, Weindruch R. (**2009**) Caloric restriction delays disease onset and mortality in rhesus monkey. *Science*, ***325***, 201-204.

[74] Ungvari Z, Sonntag WE, De Cabo R, Baur JA, Csiszar A. (**2011**) Mitochondrial protection by resveratrol. *Exercise and Sport Sciences Review*, ***39***, 128-132.

[75] Brooks CL, Gu W. **(2009**) How does SIRT1 affect metabolism, senescence and cancer? *Nature Reviews Cancer*, ***9***, 123-128.

[76] Borra MT, Smith BC, Denu JM. (**2005**) Mechanism of human SIRT1 activation by resveratrol. *Journal of Biological Chemistry*, ***280***, 17187-17195.

[77] Kaeberlein M, Mc Donagh T, Heltweg B, Hixon J, Westman EA, Caldwell SD, Napper A, Curtis R, DiStefano PS, Fields S, Bedalov A, Kennedy BK. (**2005**) Substrate-specific activation of sirtuins by resveratrol. *Journal of Biological Chemistry*, ***280***, 17038-17045.

[78] Vaquero A. (**2009**) The conserved role of sirtuins in chromatin regulation. *The International Journal of Developmental Biology*, ***53***, 303-322.

[79] Anselmi CV, Malovini A, Roncarati R, Novelli V, Villa F, Condorelli G, Bellazzi R, Puca AA. (**2009**) Association of the FOXO3A locus with extreme longevity in a southern Italian centenarian study. *Rejuvenation Research*, ***12***, 95-104.

[80] Li Y, Wang WJ, Cao H, Lu J, Wu C, Hu FY, Guo J, Zhao L, Yang F, Zhang YX, Li W, Zheng GY, Cui H, Chen X, Zhu Z, He H, Dong B, Mo X, Zeng Y, Tian XL. (**2009**) Genetic association of FOXO1A and FOXO3A with longevity trait in Han Chinese populations. *Human Molecular Genetics*, ***18***, 4897-4904.

[81] Finkel T, Deng CX, Mostoslavsky R. (**2009**) Recent progress in the biology and physiology of sirtuins. *Nature*, ***460***, 587-591.

[82] Tian Y, Ma J, Wang W, Zhang L, Xu J, Wang K, Li D. (**2016**) Resveratrol supplement inhibited the NF-κB inflammation pathway through activating AMPKα-SIRT1 pathway in mice with fatty liver. *Molecular and Cellular Biochemistry*, ***422***, 75-84.

[83] Li X. (**2013**) SIRT1 and energy metabolism. *Acta Biochim Biophys Sin (Shanghai)*, ***45***, 51–60.

[84] Dang W, Steffen KK, Perry R, Dorsey JA, Johnson FB, Shilatifard A, Kaeberlein M, Kennedy BK, Berger SL. (**2009**) Histone H4 lysine 16 acetylation regulates cellular lifespan. *Nature*, ***459***, 802-807.

[85] Vaquero A, Sternglanz R, Reinberg, D. (**2007**) NAD+ -dependent deacetylation of H4 lysine 16 by class III HDACs. *Oncogene, **26***, 5505-5520.

[86] Kobayashi Y, Furukawa-Hibi Y, Chen C, Horio Y, Isobe K, Ikeda K, Motoyama N. (**2005**) SIRT1 is critical regulator of FOXO-mediated transcription in response to oxidative stress. *International Journal of Molecular Medicine*, ***16***, 237-243.

[87] Howitz KT, Bitterman KJ, Cohen HY, Lamming DW, Lavu S, Wood JG, Zipkin RE, Chung P, Kisielewski A, Zhang LL, Scherer B, Sinclair DA. (**2003**) Small molecule activation of sirtuins extend *Saccharomyces cerevisiae* lifespan. *Nature*, ***425***, 191-196.

[88] Csiszar A. (**2011**) Anti-inflammatory effects of resveratrol: possible role in prevention of age-related cardiovascular disease. *Annals of the New York Academy of Sciences*, ***1215***, 117-122.

[89] Pacholec M, Bleasdale JE, Chrunyk B, Cunningham D, Flynn D, Garofalo RS, Griffith D, Griffor M, Loulakis P, Pabst B, Qiu X, Stockman B, Thanabal V, Varghese A, Ward J, Withka J, Ahn K. (**2010**) SRT1720, SRT2183, SRT1460, and resveratrol are not direct activators of SIRT1. *Journal of Biological Chemistry*, ***285***, 8340-8351.

[90] Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, Messadeq N, Milne J, Lambert P, Elliott P, Geny B, Laakso M, Puigserver P, Auwerx J. (**2006**) Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1*alpha*. *Cell*, ***127***, 1109-1122.

[91] Csiszar A, Labinskyy N, Pinto JT, Ballabh P, Zhang H, Losonczy G, Pearson K, de Cabo R, Pacher P, Zhang C, Ungvari Z. (**2009**) Resveratrol induces mitochondrial biogenesis in endothelial cells. *American Journal of Physiology-Heart and Circulatory Physiology*, ***297***, H13-H20.

[92] Csiszar A, Labinskyy N, Jimenez R, Pinto JT, Ballabh P, Losonczy G, Pearson KJ, de Cabo R, Ungvari Z (**2009**) Anti-oxidative and anti-inflammatory vasoprotective effects of caloric restriction in aging: role of circulating factors and SIRT1. *Mechanisms of Ageing and Development*, ***130***, 518-527.
[93] Ferrero ME, Bertelli AE, Fulgenzi A, Pellegatta F, Corsi MM, Bonfrate M, Ferrara F, De Caterina R, Giovannini L, Bertelli A. (**1998**) Activity *in vitro* of resveratrol on granulocyte and monocyte adhesion to endothelium. *The American Journal of Clinical Nutrition*, ***68***, 1208-1214.
[94] Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, Kalra A, Prabhu VV, Allard JS, Lopez-Lluch G, Lewis K, Pistell PJ, Poosala S, Becker KG, Boss O, Gwinn D, Wang M, Ramaswamy S, Fishbein KW, Spencer RG, Lakatta EG, Le Couteur D, Shaw RJ, Navas P, Puigserver P, Ingram DK, de Cabo R, Sinclair DA. (**2006**) Resveratrol improves health and survival of mice on a high-calorie diet. *Nature*, ***444***, 337-342.
[95] Pearson KJ, Baur JA, Lewis KN, Peshkin L, Price NL, Labinskyy N, Swindell WR, Kamara D,Minor RK, Perez E, Jamieson HA, Zhang Y, Dunn SR, Sharma K, Pleshko N, Woollett LA, Csiszar A, Ikeno Y, Le Couteur D, Elliott PJ, Becker KG, Navas P, Ingram DK, Wolf NS, Ungvari Z, Sinclair DA, de Cabo R. (**2008**) Resveratrol delays age-related deterioration and mimics transcriptional aspect of dietary restriction without extending life span. *Cell Metabolism*, ***8***, 157-168.
[96] Su HC, Hung LM, Chen JK. (**2006**) Resveratrol, a red wine antioxidant, possesses an insulin-like effect in streptozotocin-induced diabetic rats. *American Journal of Physiology-Endocrinology and Metabolism*, ***290***, E1339-1346.
[97] Csiszar A, Ungvari Z, Koller A, Edwards JG, Kaley G. (**2004**) Proinflammatory phenotype of coronary arteries promotes endothelial apoptosis in aging. *Physiological Genomics*, ***17***, 21-30.
[98] Hoffmann J, Haendeler J, Aicher A, Rössig L, Vasa M, Zeiher AM, Dimmeler S. (**2001**) Aging enhances the sensitivity of endothelial cells toward apoptotic stimuli: important role of nitric oxide. *Circulation Research*, ***89***, 709-715.
[99] Ungvari Z, Labinskyy N, Gupte S, Chander PN, Edwards JG, Csiszar A. (**2008**) Dysregulation of mitochondrial biogenesis in vascular endothelial and smooth muscle cells of aged rats. *American Journal of Physiology-Heart and Circulatory Physiology, **294***, H2121-H2128.
[100] Virgil M, Contestabile A. (**2000**) Partial neuroprotection of *in vivo* excitotoxic brain damages by chronic administration of the red wine antioxidant agent, trans-resveratrol in rats. *Neuroscience Letters, **281***, 123-126.
[101] Gao ZB, Hu GY. (**2005**) Trans-resveratrol, a red wine ingredient, inhibits voltage-activated potassium currents in rat hippocampal neurons. *Brain Research*, ***1056***, 68-75.
[102] Li M, Wang QS, Chen Y, Wang ZM, Liu Z, Guo SM. (**2005**) Resveratrol inhibits neuronal discharges in rat hippocampal CA1 area. *Sheng Li Xue Bao, **57***, 355-360.
[103] Shetty AK. (**2011**) Promise of resveratrol for easing status epilepticus and epilepsy. *Pharmacology & Therapeutics*, ***131***, 269-286.
[104] Sun AY, Chen YM, James-Kracke M, Wixom P, Cheng Y. (**1997**) Ethanol-induced cell death by lipid peroxidation in PC12 cells. *Neurochemical Research*, ***22***, 1187-1192.
[105] Jang JH, Surh YJ. (**2003**) Protective effect of resveratrol on *beta*-amyloid-induced oxidative PC12 cell death. *Free Radical Biology and Medicine*, ***34***, 1100-1110.
[106] Han YS, Zheng WH, Bastianetto S, Chabot JG, Quirion R. (**2004**) Neuroprotective effects of resveratrol against *beta*-amyloid-induced neurotoxicity in rat hippocampal neurons: involvement of protein kinase C. *British Journal of Pharmacology*, ***141***, 997-1005.
[107] Zhang F, Shi JS, Zhou H, Wilson B, Hong JS, Gao HM. (**2010**) Resveratrol protects dopamine neurons against lipopolysaccharide-induced neurotoxicity through its anti-inflammatory actions. *Molecular Pharmacology*, ***78***, 466-477.
[108] Liu C, Shi Z, Fan L, Zhang C, Wang K, Wang B. (**2011**) Resveratrol improves neuron protection and functional recovery in rat model of spinal cord injury. *Brain Research*, ***1374***, 100-109.
[109] Maher P, Dargusch R, Bodai L, Gerard PE, Purcell JM, Marsh JL. (**2011**) ERK activation by the polyphenols fisetin and resveratrol provides neuroprotection in multiple models of Huntington's disease. *Human Molecular Genetics*, ***20***, 261-270.
[110] Shindler KS, Ventura E, Dutt M, Elliott P, Fitzgerald DC, Rostami A. (**2010**) Oral resveratrol reduces neuronal damage in a model of multiple sclerosis. *Journal of Neuro-Ophthalmology*, ***30***, 328-339.
[111] Marx W, Kelly JT, Marshall S, Cutajar J, Annois B, Pipingas A, Tierney A, Itsiopoulos C. (**2018**) Effect of resveratrol supplementation on cognitive performance and mood in adults: a systematic literature review and meta-analysis of randomized controlled trials. *Nutrition Reviews*, ***76***, 432-443.
[112] Lombardi G, Vannini S, Blasi F, Marcotullio MC, Dominici L, Villarini M, Cossignani L, Moretti M. (**2015**) *In vitro* safety/protection assessment of resveratrol and pterostilbene in a human hepatoma cell line (HepG2). *Natural Product Communications*, ***10***, 1403-1408.
[113] Patel KR, Scott E, Brown VA, Gescher AJ, Steward WP, Brown K. (**2011**) Clinical trials of resveratrol. *Annals of the New York Academy of Sciences*, ***1215***, 161-169.
[114] Almeida L, Vaz-da-Silva M, Falcão A, Soares E, Costa R, Loureiro AI, Fernandes-Lopes C, Rocha JF, Nunes T, Wright L, Soares-da-Silva P. (**2009**) Pharmacokinetic and safety profile of trans-resveratrol in a rising multiple-dose study in healthy volunteers. *Molecular Nutrition & Food Research*, ***53***, S7-S15.
[115] Boocock DJ, Faust GE, Patel KR, Schinas AM, Brown VA, Ducharme MP, Booth TD, Crowell JA, Perloff M, Gescher AJ, Steward WP, Brenner DE. (**2007**) Phase I dose escalation pharmacokinetic study in healthy volunteers of resveratrol, a potential cancer chemopreventive agent. *Cancer Epidemiology, Biomarkers & Prevention*, ***16***, 1246-1252.
[116] Brown VA, Patel KR, Viskaduraki M, Crowell JA, Perloff M, Booth TB, Vasilinin G, Sen A, Schinas AM, Piccirilli G, Brown K, Steward WP, Gescher AJ, Brenner DE. (**2010**) Repeat dose study of the cancer chemopreventive agent resveratrol in healthy volunteers: safety, pharmacokinetics and effect on the insulin-like growth factor axis. *Cancer Research*, ***70***, 9003-9011.
[117] La Porte C, Voduc N, Zhang G, Seguin I, Tardiff D, Singhal N, Cameron DW. (**2010**) Steady-State pharmacokinetics and tolerability of *trans*-resveratrol 2000 mg twice daily with food, quercetin and alcohol (ethanol) in healthy human subjects. *Clinical Pharmacokinetics*, ***49***, 449-454.
[118] Shukla Y, Singh R. (**2011**) Resveratrol and cellular mechanisms of cancer prevention. *Annals of the New York Academy of Sciences*, ***1215***, 1-8.
[119] Tyihák E, Király-Véghely Z, Móricz AM. (**2011**) Multiple beneficial effects of resveratrol and their chemical-biochemical basis. *Natural Product Communications*, ***6***, 631-638.
[120] Canturk Z, Dikmen M, Artagan O, Ozarda MG, Ozturk N. (**2016**) Cytotoxic effects of resveratrol, rutin and rosmarinic acid on ARH–77 human (multiple myeloma) cell line. *Natural Product Communications*, ***11***, 1441-1444.
[121] Pyo K-H, Lee Y-W, Lee S-H, Xin C-F, Shin J-H, Shin EH. (**2017**) Preventive effects of resveratrol-enriched extract of peanut sprout on bacteria- and estradiol-induced prostatitis in mice. *Natural Product Communications*, ***12***, 73- 78.
[122] Sintuyanon N, Phoolcharoen W, Pavasant P, Sooampon S. (**2017**) Resveratrol demonstrated higher antiproliferative and antiangiogenic efficacy compared with oxyresveratrol on head and neck squamous cell carcinoma cell lines. *Natural Product Communications*, ***12***, 1781-1784.
[123] Dybkowska E, Sadowska A, Świderski F, Rakowska R, Wysocka K. (**2018**) The occurrence of resveratrol in foodstuffs and its potential for supporting cancer prevention and treatment. A review. *Roczniki Państwowego Zakładu Higieny*, ***69***, 5-14.
[124] Kudo T, Narisawa T, Abo S. (**1980**) Antitumor activity of indomethacin on methylazoxymethanol-induced large bowel tumors in rats. *Gann*, ***71***, 260-264.

[125] Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CW, Fong HH, Farnsworth NR, Kinghorn AD, Mehta RG, Moon RC, Pezzuto JM. (**1997**) Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science*, ***275***, 218-220.
[126] Garvin S, Ollinger K, Dabrosin C. (**2006**) Resveratrol induces apoptosis and inhibit angiogenesis in human breast cancer xenografts *in vivo*. *Cancer Letters*, ***231***, 113-122.
[127] Kalra N, Roy P, Prasad S, Shukla Y. (**2008**) Resveratrol induces apoptosis involving mitochondrial pathways in mouse skin tumorigenesis. *Life Sciences*, ***82***, 348-358.
[128] Kundu JK, Surh YJ. (**2004**) Molecular basis of chemoprevention by resveratrol: NF-*kappa*B and AP-1 as potential targets. *Mutation Research*, ***555***, 65-80.
[129] Liao D, Johnson RS. (**2007**) Hypoxia: a key regulator of angiogenesis in cancer. *Cancer and Metastasis Reviews*, ***26***, 281-290.
[130] López-Lázaro M. (**2006**) Hypoxia-inducible factor 1 as a possible target for cancer chemoprevention. *Cancer Epidemiology, Biomarkers & Prevention*, ***15***, 2332-2335.
[131] Hickey MM, Simon MC. (**2006**) Regulation of angiogenesis by hypoxia and hypoxia-inducible factors. *Current Topics in Developmental Biology*, ***76***, 217-257.
[132] North S, Moenner M, Bikfalvi A. (**2005**) Recent developments in the regulation of the angiogenic switch by cellular stress factors in tumors. *Cancer Letters*, ***218***, 1-14.
[133] Gatouillat G, Balasse E, Joseph-Pietras D, Morjani H, Madoulet C. (**2010**) Resveratrol induces cell-cycle disruption and apoptosis in chemoresistant B16 melanoma. *Journal of Cellular Biochemistry*, ***110***, 893-902.
[134] Cheng TM, Chin YT, Ho Y, Chen YR, Yang YN, Yang YC, Shih YJ, Lin TI, Lin HY, Davis PJ. (**2018**) Resveratrol induces sumoylated COX-2-dependent anti-proliferation in human prostate cancer LNCaP cells. *Food and Chemical Toxicology*, ***112***, 67–75.
[135] Gupta SC, Kannappan R, Reuter S, Kim JH, Aggarwal BB. (**2011**) Chemosensitization of tumors by resveratrol. *Annals of the New York Academy of Sciences*, ***1215***, 150-160.
[136] Higgins CF. (**2007**) Multiple molecular mechanisms for multidrug resistance transporters. *Nature*, ***446***, 749-757.
[137] Bharti AC, Shishodia S, Reuben JM, Weber D, Alexanian R, Raj-Vadhan S, Estrov Z, Talpaz M, Aggarwal BB. (**2004**) Nuclear factor-*kappa*B and STAT3 are constitutively active in CD138+ cells derived from multiple myeloma patients, and suppression of these transcription factors leads to apoptosis. *Blood*, ***103***, 3175-3184.
[138] Niedzwiecki A, Roomi MW, Kalinovsky T, Rath M. **(2016**) Anticancer efficacy of polyphenols and their combinations. *Nutrients*, ***8***, 1-17.
[139] Asensi M, Medina I, Ortega A, Carretero J, Baño MC, Obrador E, Estrela JM. (**2002**) Inhibition of cancer growth by resveratrol is related to its low bioavailability. *Free Radical Biology and Medicine, **33***, 387-398.
[140] Carter LG, D`Orazio JA, Pearson KJ. (**2014**) Resveratrol and cancer: focus on *in vivo* evidence. *Endocrine-Related Cancer*, ***21***, R209–R225.
[141] Hao J, Tuck AR, Sjödin MOD, Lindberg J, Sand A, Niklasson B, Argyraki M, Hovatta O, Damdimopoulou P. (**2018**) Resveratrol supports and *alpha*-naphthoflavone disrupts growth of human ovarian follicles in an *in vitro* tissue culture model. *Toxicology and Applied Pharmacology*, ***338***, 73-82.