Resveratrol, human health and winemaking perspectives

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Abstract: Resveratrol, (3, 5, 4'-trihydroxystilbene) is a non-flavonoid polyphenol stilbene synthesized by plants when damaged by infectious diseases or ionizing radiation. Although present in more than seventy plant species, grapes and wine are the major dietary contributors of resveratrol, responsible for 98% of the daily intake. In 1992, Renaud and De Lorgeril first linked wine polyphenols, including resveratrol, to the potential health benefits ascribed to regular and moderate wine consumption (the so called "French Paradox"). Since then, resveratrol has received increasing scientific interest, leading to research on its biological actions, and to a large number of published papers, which have been collected and discussed in this review. The relatively low amounts of resveratrol measured in wine following moderate consumption, however, may be insufficient to mitigate biological damage, such as that due to oxidative stress. On this basis, the authors also highlight the importance of viticulture and the winemaking process to enhance resveratrol concentrations in wine in order to bolster potential health benefits.

Keywords; Resveratrol, wine and health, oxidative stress, winemaking

Introduction

It is well known that a healthy diet is one of the most potent tools to avoid any kind of malnutrition, as well as to reduce risk factors for chronic pathologies such as cancer, cardiovascular diseases, diabetes and dementia. A balanced diet must supply the suitable amount of energy and nutrients to maintain the desirable body weight and homeostasis. In this

regard, several national and international guidelines have been published to guide the choices of consumers and public organizations (EFSA; 2017; JECFA, 2003; USDA, 2015), In the last few decades, besides the nutritional balance, a relatively new concept on the proper intake with the diet of functional compounds (for example antioxidants such as polyphenols) has been introduced; in fact, while not providing energy, they can contribute critically to the general health of consumers (Vanzour et al., 2010; Cvejic and Gojkovic-Bukarica, 2016).

Aging and, consequently, chronic non-transmissible or lifestyle diseases such as cardiovascular diseases, diabetes, oncological and neurodegenerative diseases, start as functional problems many years before their clinical manifestations. Aging as a concept of use and wear, as well as an accumulation of damages in molecular structures over time have a common denominator, namely, oxidative stress. Oxidative stress is an increase in free radical production and/or a decrease in the production of antioxidant molecules (Sies, 1985; Hernández Saavedra and Mc Cord, 2007; Pisoschi and Pop, 2015). Cellular biology covers the energy demands of metabolism through organelles such as mitochondria. In order to accomplish this mitochondria, which can be considered as chemical machines, work at constant pressure and temperature to produce energy (adenosine triphosphate or ATP) 24 hours a day, which is used in energy exchanges. As part of this energy production process, however, mitochondria also produce metabolic waste, that is, oxygen free radicals (OFR). One to three percent of the oxygen that cells breathe (which is equivalent to 4 to 12 liters of oxygen/day for humans) leaks from the respiratory mitochondrial chain, goes through their membrane and remains in the cell as OFR (Boveris et al., 1972), producing an accumulation of acid waste, molecular damages, diseases and aging (Boveris, 2005; Raha and Robinson, 2000). Therefore, mitochondria, the main source of cellular energy, are also the source of 95% of the body's OFR (Stotland and Gottlieb, 2015). Correspondingly, evolving biology has

adapted by means of a system of "antioxidant defense" inside the intracellular compartment to protect itself from damages caused by its own functioning (Table 1).

Unlike intracellular spaces, the antioxidant defenses of intravascular and intestinal lumen spaces depend almost exclusively on the food supply, which makes them vulnerable to oxidative stress if the supply is 'unsuitable'. In other words, the lifestyle-related prevention is greatly significant to fight the redox imbalance. As Table 1 shows, the intracellular antioxidant defense system is dual and based on endogenous enzymatic system and a non-enzymatic foodborne system. Eventually, the enzymatic system is defeated by the damage produced by OFR, causing an increase of oxidative stress (Sies, 1985; Hernández Saavedra and McCord, 2007; Pisoschi and Pop, 2015). It has been shown that after 20 years of age, intracellular antioxidant defenses as measured by glutathione concentration start decreasing at approximately 1.2% per year due to OFR damage (Samiec et al, 1998; Maher, 2005). Therefore, oxidative stress caused by OFR is the side-effect of energy production due to the comburent used, which is oxygen (Barja, 2014). As shown in Figure 1, during human life, three stages can be potentially identified in redox homeostasis: the first one is 'full health' period, up to 28 to 30 years old, when antioxidant defenses are balanced in number with pro-oxidant molecules. The second stage is the 'healthy' period (apparent wellbeing), between 30 and 60 years old, when there is a redox imbalance with oxidative stress produced by the deterioration associated with aging, being sedentary, overweight or obesity, an increased and unbalanced plasma cholesterol concentration, and physical or psychological stress. During this stage, the 'healthy' situation is relative due to redox imbalance and lifestyle-related prevention is greatly significant. After turning approximately 60 years old, a third stage begins called 'illness' period with possible clinical manifestations.

As shown in Figure 2, during this third stage (illness), total oxidative stress is the sum of what has been provided by cellular breathing (level 1), oxidative stress by physiological stimulation (e.g. postprandial) (level 2), metabolic waste and other disease risk factors such as high blood pressure, obesity, dyslipoproteinemia, chronic inflammatory processes and diabetes mellitus (levels 3 to 6).

The measurement of the body's antioxidant defenses could become usual practice in the future to evaluate risk factors for chronic diseases, in addition to blood pressure and body weight. For example, a quantification of skin carotenoids by resonance Raman Spectroscopy has been suggested by Mayne et al. (2013). A decrease in antioxidant defenses may act as an alert to change dietary practices or to use antioxidant dietary supplements to reduce the risk of cardiovascular, metabolic or neurodegenerative diseases, as well as that of cancer. Non-invasive Raman Spectroscopy is a technique that can be used to measure antioxidant defenses (Ermakov and Gellerman, 2010).

As cells do not have antioxidant reserves, if intestinal digestion causes oxidative stress and there is not an appropriate dietary antioxidant balance, the cellular structures of the internal milieu may be damaged (Rahal et al., 2014).

Potential benefits of drinking red wine with meals have been partly ascribed to wine's relatively large content of polyphenols such as resveratrol (Das and Das, 2010). Polyphenols have been shown to reduce the damaging effects of OFR during food digestion and absorption (Karatzi et al., 2008). Nourishment may become a risky habit, therefore, if there is not an appropriate redox balance in nutrients.

Resveratrol

Resveratrol (3, 5, 4′-trihydroxystilbene) is a phytoalexin, non-flavonoid polyphenol present in more than 70 plant species. Only a few of these plants are edible and among the latter, the

most important are: *Vitis vinifera* (grape), *Arachis hypogaea* (peanut), *Theobroma cacao* (cacao), plants producing berries (*Vaccinium myrtillus*, *Ribes nigrum*, *Rubus idaeus*, etc) and their relative by-product (such as red wine, chocolate, juices, etc.). It has been shown that resveratrol has *in vitro* anti-inflammatory effects and, accordingly, has been used as dietary supplement in animal models to increase longevity and improve health in mice fed with high caloric content (Baur et al., 2006; Birrell et al., 2005; Rahman, 2006). Dietary studies in animal models have shown that resveratrol and other chemically related compounds activate SIRT1 (Cantó and Auwerks, 2012; Timmer et al., 2012), and imitate the effects of caloric restriction (Lee and Min, 2013; Wu and Hsieh, 2011); sirtuins are a family of deacetylase enzymes that, when activated, silence DNA information. The interest in resveratrol in nutrition and medicine started in 1992, when resveratrol was identified as a possible explanation for cardiovascular protective effects associated with the intake of red wine in "The French Paradox" (Siemann and Creasy, 1992; Renaud and De Lorgeril, 1992). One potential cardioprotective mechanism of action is the inhibition of low density lipoprotein (LDL) oxidation (Frankel et al., 1993; Frankel et al., 1995). Potential cancer preventive effects have also been proposed for resveratrol (Jang et al., 1997; Carter et al., 2014; Xue et al., 2014). Such data increased the interest of scientists, the general public and the pharmaceutical and dietary supplement industries, where a bibliographic search in Pubmed using ‘resveratrol’ as the keyword currently delivers more than 9,000 publications.

Numerous research efforts explored resveratrol’s biological mechanisms of actions. There are, however, certain limitations that create doubts when extrapolating the results of basic *in vitro* and *ex vivo* research to human health. For example, basic research often involves dietary interventions with relatively high doses of resveratrol compared to those naturally found in wine (Linn et al., 2016; Wong et al., 2016).

It is well known that the food matrix is important in modifying intestinal absorption, bioavailability, pharmacokinetics of molecules and, as a consequence, animal and human health outcomes (Stockley et al., 2012). In general, lipophilic resveratrol has been shown to be highly absorbed after oral ingestion and extensively and rapidly metabolised through glucuronidation and sulfatation reactions in the liver, and also through hydrogenation of the aliphatic double bond in the intestine (Soleas et al., 2001; Meng et al., 2004; Goldberg et al., 2003; Walle et al., 2004). Human studies by Walle et al. (2004) on the oral absorption of ^{14}C-resveratrol showed that the elimination half-life of total resveratrol metabolites is about 6 to 15 hours after oral doses. Resveratrol metabolites can be detected in the urine of humans consuming one glass of wine per week, if the last drink was consumed three days previously, or in those consuming three glasses of wine per week, if the last drink was consumed five days previously (Zamora-Ros et al., 2006; Zamora-Ros et al., 2009).

Despite its low bioavailability, resveratrol may show efficacy *in vivo* through its metabolites or derivatives (Stockley et al., 2012). In plasma, unmetabolised resveratrol binds to both albumin and lipoproteins such as LDL (Gambini et al., 2015). These complexes, in turn, can be dissociated at cellular membranes, which have receptors for albumin and LDL, leaving the resveratrol free and allowing it to enter cells. Accordingly, resveratrol may interact with extracellular and intracellular molecules, and its mechanism of action at the cellular level may be triggered by either activating signaling pathways, when binding to cell membrane receptors, activating intracellular mechanisms, or even developing its effects inside the nucleus. In addition, its efficacy may also be explained by the conversion of both sulfates and glucuronides back to resveratrol in target organs, such as the liver and intestine (Vitrac et al., 2003; Wenzel and Somoza, 2005). In addition, *in vivo* effects may be attributable to its bioactive metabolites, which are measurable in plasma and urine post oral ingestion (Vitaglione et al., 2005, Boocock et al., 2007).

Resveratrol daily intake

Different studies have calculated the daily dietary intake of resveratrol or total stilbenes, but results are not always in agreement (Rabassa et al., 2015; Siemann and Creasy, 1992; Zamora-Ros et al., 2006; Zamora-Ros et al., 2008; Zamora-Ros et al., 2009; Zamora-Ros et al., 2012). According to a relatively recent study (Rabassa et al., 2015), the daily intake of total resveratrol (total stilbenes) is in the order of few mg/day, where red wine is the richest source (approximately 90%).

Resveratrol and human health: criteria for literature search

In this review, papers reporting human studies on resveratrol intake and benefits are collected and discussed, according to the body of evidence. Two of the most important scientific databases of references and abstracts on life sciences and biomedical topics, PubMed/MEDLINE and Embase, were systematically searched to create the present work. The following search strategy and selection criteria were used: data were collected from database inception to April 2017, with the terms “clinical trial”, “benefits”, “health”, in combination with “resveratrol”. Additional search criteria were: human study; oral exposure; and controlled trial.

Results

Since 2009, there has been a proliferation of resveratrol-related dietary interventions in patients treated for different pathologies and in healthy volunteers with risk factors. Searches from 1970 to 2008 produced mainly studies performed *in vitro* or in laboratory animals. The papers selected according to the inclusion criteria are listed in Table 2.

The Spanish PREDIMED study was one of the first studies to assess the association between moderate wine consumption, resveratrol intake and cardiovascular (CVD) risk factors in 1000 participants including high cardiovascular risk patients (Zamora-Ros et al., 2012). Measuring the total resveratrol metabolites (TRMs) in urine as biomarkers of exposure, the authors showed that moderate wine consumption as well as resveratrol intake can positively modulate some recognized CVD risk factors, such as blood lipid profiles, fasting blood glucose (significant changes only with resveratrol) and heart rate. Data collected indicated that resveratrol intake (as such or with wine) might help to decrease CVD risk factors.

A second study by Semba et al. (2014), assessed whether dietary resveratrol intake, but not specifically wine consumption, modulated events associated with inflammation, CVD, cancer and mortality. It was a prospective cohort study involving 783 community-dwelling men and women aged 65 years or older in two villages of the Chianti area, from 1998 to 2009. Urines were analysed to measure the level of resveratrol metabolites (URM), and population was classified in quartiles: <1554 (n= 195), 1554-4996 (n= 196), 4996-15010 (n= 196), and >15010 (n= 196) nmol URM/ g creatinine. During the nine years of follow-up, 268 (34.2%) of the perticipants died. The relationship between URM and all-cause of mortality was statistically evaluated and no significant correlation was found, when the model was adjusted for age, sex, BMI, serum level of lipids, and chronic diseases. In details, no differences was observed between quartiles for hearth failure, periferal artery disease, stroke, diabetes melitus, cancer, chronic kidney disease, and overall mortality.

To better evaluate the result of the study, the authors calculated the average daily dietary consumption of resveratrol in this population during the follow up. The mean log dietary intake of resveratrol (mg) were: -2.71 (- 2.87 to -2.55) at 3 months; -2.82 (-2.99 to -2.64) at 6 months; and – 2.66 (-2.81 to -2.50) at 9 months. This amount appeared insufficient to have a significant influence on health status and mortality risk of participants. Moreover, the lack of

the expected association may reflect variability in resveratrol intake, inter-individual variation, and variability of host-gut microbiota (Blaut and Clavell, 2007; Nicholson et al., 2012) indicating that a much larger sample size is required to reach final conclusions.

These contradictory studies, therefore, suggest that the next research step is the identification of an effective 'dose' of resveratrol necessary to benefit human health. Summarizing the data collected in this paper (Table 3 and 4), the most significant beneficial health effects are associated with the cardiovascular system. The lowest active amount of resveratrol identified was 30 mg/day to improve endothelial function in healthy individuals (Wong et al., 2011). A wide range of resveratrol 'doses' has been associated with the improvement of other physiological/pathological functions and parameters or reduction of risk factors.

The effects of viticulture and winemaking practices on resveratrol concentrations in wine

Resveratrol exists in both *cis* and *trans* forms in wine, but *trans*-resveratrol predominates in grapes and may be methylated and polymerized to produce piceid, pterostilbene and the viniferins, respectively, and glycosylated during fermentation (Jeandet et al., 1995a; Langcake, 1981; Pezet and Cuenat, 1996). The average concentration of total resveratrol in red wine is 7 mg/L and is 2 mg/L in rosé and 0.5 mg/L in white wine, but ranges widely according to grape variety, geographical indication and vintage (Waterhouse, 2002). In contrast to other grape-derived phenolic compounds produced in the skins and seeds of grapes in response to increased sunlight and temperature (Spayd et al., 2002), resveratrol acts like a phytoalexin and is produced by the skin cells of grapes and by the leaves in response to *Botrytis cinerea, Plasmopara viticola, Rhizopus stolonifer, Uncinula necator* and other fungal infections on grapevines, as well as in response to UV light, radiation and related external stimuli (Ector et al., 1996; Adrian, 2000; Gershman et al., 1954). Resveratrol is also

synthesized by unstressed vines but to a significantly lesser degree (Pezet et al., 1996). Disease-resistant plant genotypes quickly produce and accumulate resveratrol while in susceptible species, such as *Vitis vinifera*, production occurs more slowly. The cultivar Pinot Noir appears quite susceptible to fungal infection and hence generally produces and accumulates a higher concentration of resveratrol than other varieties, irrespective of viticultural origin (Siemann and Creasy, 1992; Goldberg et al., 1995, Jeandet et al., 1995b).

Accordingly, a high concentration of resveratrol has been consistently measured in wines from cooler climate regions reflecting a cool damp climate and increased fungal pressure, such as Ontario in Canada, and Bordeaux and the Rhone Valley in France, although some sub-regional differences were also observed (Goldberg et al., 1995; Soleas et al., 1997). Conversely, a significantly lower concentration of resveratrol has been measured in wines from relatively warm and dry climates. In grape berries infected with powdery mildew, however, the concentration of resveratrol appears to be correlated with the fungal pressure (Romero-Perez et al., 2001). Studies suggest also that although the synthesis of resveratrol is induced and increases as climatic conditions lead to *Botrytis cinerea* infection, excessively heavy infection actually degrades the induced resveratrol by activating an exocellular laccase-like stilbene oxidase, so that a relatively low concentration of resveratrol is measured in wines from a vintage where there is heavy *Botrytis cinerea* pressure (Pezet et al., 1991; Jeandet et al., 1995b).

In nutraceutical research, ultrasonication techniques have been applied to enhance the accumulation of secondary metabolites in plants. Ultrasonication techniques have recently been applied to increase the accumulation of resveratrol in grape skins and leaves (Hasan and Baek, 2013). The accumulation of resveratrol increased in grape skin by 7.7-fold after ultrasonication treatment for 5 minutes, followed by incubation for a further 6 hours. The increase of resveratrol in leaves, however, was less than that in grape skin. The amount of

increased resveratrol in grape leaves after 15 minutes of ultrasonication, followed by a 3-hour incubation, was 1.8-fold higher than that observed in non-treated controls. The accumulation of resveratrol in both grape skin and leaves was dependent on the ultrasonication time and the incubation period. Resveratrol-enriched grape juice has also been observed using ultrasonication treatment reported in previous work (Hasan et al., 2014). In all the grape varieties used, significantly higher amounts of resveratrol were observed in grape juice manufactured from fruit treated with ultrasonication of the grape skins of cultivars Campbell Early, MBA, and Kyoho:; the content of resveratrol in juices increased by 1.53, 1.15, and 1.24 times, respectively.

The concentration of phenolic compounds in wine is also influenced by winemaking variable (Revilla et al., 2001). The extraction of total phenolic compounds during winemaking from the skins, seeds and flesh of grape berries into must, however, rarely exceeds 50% of the total amount present originally in the grape (Somers and Vérette, 1988). In general, white wine is made by fermenting juice from which grape skins and seeds have been removed, and red wine is made by fermenting juice in the presence of grape skins and seeds. Fermentation with solid grape material allows the aqueous and alcoholic extraction of phenolic compounds from the skins and seeds. The concentration of total phenolic compounds in wine consequently increases during fermentation with skins and seeds, but may subsequently decrease as some of the phenolic compounds combine with proteins and yeast hulls and precipitate. The concentration of total phenolic compounds continues to decrease with fining and filtration, and during maturation.

As phenolic compounds are primarily located in the skins and seeds of grape berries, it is implicit that winemaking practices, which influence the extraction of these compounds from the skins and seeds into the wine, would influence their concentration in the final wine.

The influence of winemaking techniques in conjunction with grape variety on the resveratrol concentration in wines has also been studied for the cultivars Merlot, Cabernet Sauvignon and Prokupac as well as for Pinot Noir (Atanacković et al., 2012). Applied winemaking technologies included thermovinification and the separation of must from pomace. The total resveratrol concentration in analysed wine samples ranged from 0.35 to 4.85 mg/L. Merlot wines had the highest average resveratrol concentration, while the lowest was found for the native cultivar Prokupac.

Although resveratrol concentrations in the red wines depended on the grape variety, correlation between the applied winemaking technology and the concentration of resveratrol in wines was not observed. Data suggests, however, that the most important factor in winemaking is the maceration time, since the highest concentrations of resveratrol and piceid, and the highest antioxidant activity were found following six and ten days of maceration for Vranec and Merlot wines (Kostadinović et al., 2012). In addition, the techniques of skin extraction and enzymatic hydrolysis of glucoside forms play an important role in resultant resveratrol concentration of wine, because stilbenes compounds are mainly found in skin cells of the berry (Bavaresco et al., 2012).

To enhance resveratrol concentrations in wine pre and post fermentation, must could be enriched with resveratrol-rich grape skins and press wine could be added to free run juice.

Alternatively, grape-derived resveratrol could simply be added during winemaking; however this practice is not allowed in all countries. Sulfur dioxide is added during winemaking to inhibit the growth of unwanted yeasts and bacteria, and to protect wine from oxidation. Sulfur dioxide is, however, associated with allergies and sensitivities in susceptible individuals, which is reflected in mandated warning labelling for added amounts greater than 10 mg/L (Stockley and Johnson, 2015). Consequently, alternatives to sulfur doxide are being sought. A pilot study assessed the replacement of sulfur dioxide with the antioxidant resveratrol during

winemaking (Pastor et al., 2015). Two different amounts of resveratrol (150 mg/L and 300 mg/L), along with reduced or no sulfur dioxide added during winemaking (Pastor et al., 2015), had similar effects on the organoleptic or sensory properties of the resultant wine. The benefical effects of adding resveratrol to reduce or replace sulfur dioxide is two-fold for consumers ─ a reduced risk of an adverse reaction with a potentially reduced risk of mortality.

Conclusions

The oxidative stress is an imbalance between antioxidant molecules production and the oxygen reactive species, which are a natural consequence of cellular breathing that produces energy and is performed in mitochondria. This homeostasis is a delicate balance in molecular biology aimed to maintain the suitable Redox potential. If the redox potential increases, it means that we are facing an increased production of oxygen free radicals, which is one of the first risk factors of non-transmissible chronic diseases of aging and its consequences like cardiovascular, metabolic and neurodegenerative diseases and cancer. Given that the world's population is growing at an unprecedented rate, where percentage of people worldwide aged 65 and over is projected to double to approximately 17 percent of the world's population by 2050 (He et al.. 2016), research into simple dietary interventions to reduce the risk these chronic diseases have become increasingly important. Resveratrol has been consistently shown to be a biologically active compound since 1992, having potential effects on human health and diseases. Wine is the main sources of dietary resveratrol although average intake is in the order of few mg/day and it is not enough to support healthy biological actions. Therefore, we need to thoroughly investigate resveratrol's effects in humans and explores means to increases its concentration to be biologically relevant in foods (mainly fruits and derivatives) and beverages (such as juices and wine).

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ABBREVIATIONS

ALT=Alanine aminotransferase

AMPK=AMP-activated protein kinase

APC= Antigen presenting cells

ApoB100=Apolipoprotein B100

ApoB48=Apolipoprotein B48

AUC=Area Under the Curve

BMI=Body Mass Index

BNP=Brain natriuretic Peptide

CAD=Coronary Artery Disease

CCL3=Chemokine (C-C motif) ligand 3

CCND2= G1/S specific cyclin-D2 gene

CF=calcium fructoborate

CRP=C-reactive protein

CVD=Cardiovascular disease

CYP1A2=Cytochrome P450 1A2

CYP2D6 =Cytochrome P450 2D6

CYP3A4=Cytochrome P450 3A4

FMD=Flow Mediated Dilatation

GE=Grape extract

GE-RES=Grape-extract resveratrol

GLP1=Glucagon-like peptide 1

HbA1c= Glicated hemoglobin

HDL=High Density Lipoprotein

HDLcol=cholesterol-HDL

Hs-CRP=high sensitive C reactive protein

IGF-1=Insulin like grow factor 1

IGFBP3= Insulin like grow factor binding protein 3

IL-10=Interleukin-10

IL-6=Interleukin-6

LDL=Low Density Lipoproteins

LDLcol=cholesterol-LDL

NAMPT=Nicotinamide phosphoribosyltransferase

NF-kB=Nuclear Factor –kB

NO=Nitric Oxide

OFR= Oxygen Free Radicals

Ox-LDL=Oxidized-LDL

PAI-1=Plasminogen activator inhibitor-1

PBMCs=Peripheral Blood Mononuclear Cells

PGC1=Peroxisome proliferator activated receptor gamma coactivator 1

PPARGC1A=Peroxisome Proliferator Activated Receptor Gamma Coactivator 1 alpha

RASSSF-1=Ras association domain-containing protein 1-alpha gene

RES=Resveratrol

SIRT1=Sirtuin 1

T2DM=Type 2 Diabetes mellitus

TNF-alpha=Tumor necrosis alfa

UC=Ulcerative colitis

UF=Ultrafiltrate

Table 1: Antioxidant defense systems in intracellular, intravascular and intestinal lumen spaces

Source of antioxidant defense	**Specific molecule**	**Intracellular space**	**Intravascular space**	**Intestinal lumen**
Endogenous enzymes	Catalase	X		
	Glutathione peroxidase	X		X
	Superoxide dismutase	X		
Endogenous antioxidant	Glutathione	X		
Active molecules from food	Carotenes	X	X	X
	Vitamin C	X	X	X
	Vitamin E	X	X	X
	Polyphenols	X	X	X

Modified from Boveris, 2004

Table 2. Overview of selected studies regarding resveratrol-related dietary interventions from 1970 to 2016

	Cohort, sample size (n)	**Trial type**	**Resveratrol dosage**	**Duration**	**Target**	**Main outcome**	**Reference**
1	Patients with colon cancer (n=8).	Four parallel arms, randomized trial. Uncontrolled and open trial.	Daily intake of: 80 g grape powder (GP) with 0.07 mg RES, n=3; or 120 g GP with 0.11 mg RES, n=2; or 3.9 mg RES + 120 mg quercetin, n=2; or 15.5 mg RES + 480 mg quercetin, n=1.	19 days	Changes in Wnt singnalling pathway in normal and cancer colon tissues after surgery.	Inhibition of some genes from Wnt signalling pathway only in normal tissue.	Nguyen et al., 2009
2	Patients with colorectal cancer (n=20).	Two parallel arms, non-randomized, blind, placebo uncontrolled.	RES daily dose: 0.5 g, n=10; or 1 g, n=10. RES in capsules.	8 days	Detection of RES and metabolites in colorectal tissue, and effect on proliferation marker Ki-67.	Ki-67 antigen level was reduced by 5% and 7% in cancer and normal tissue, respectively.	Patel et al., 2010
3	Patients with colorectal cancer and hepatic metastasis (n=6).	Patients with colorectal cancer and hepatic metastasis (n=6). Two parallel arms, randomized, placebo.	Preoperative daily intake of a sachet containing 5 g of RES or placebo.	From 10 to 21 days	Pharmacokinetics, tissue disposition and effect on apoptosis marker (cleaved caspase-3).	Detection of RES in hepatic tissue and increased (39%) content of cleaved caspase-3 in this tissue.	Howells et al., 2011
4	Twenty over weight or obese male subjects (age: 36.6-61 yrs) with non-alcoholic fatty liver disease.	Open study, placebo-controlled.	Placebo or 3000 mg RES daily. Daily dose: 3 cps (500 mg) before breakfast and before bedtime (total 6 cps). They were instructed to maintain their lifestyle habits.	8 weeks	To determine if RES improves the parameters of non-alcoholic fatty liver disease.	RES was well tolerated, although there were no significant results in insulin function, steatosis, or abdominal fat distribution. There were no changes in plasma markers of inflammation.	Chachay et al., 2014
5	60 subjects with non alcoholic fatty liver disease.	Double-blind, randomized, placebo-controlled trial.	Subjects were given placebo or 2 cps containing 150 mg RES, twice daily.	3 months	To evaluate the effect of RES on insulin resistance, glucose, epatic enzymes and lipid metabolism in nonalcoholic fatty liver disease.	RES significantly decreased aspartate aminotransferase, glucose and LDL cholesterol	Chen et al., 2015

6	49 patients (15 females) with a history of non alcoholic fatty liver disease. Mean age of 45.16.	Randomized, double-blinded, placebo-controlled.	Placebo or 500 mg/day of RES.	12 weeks	To determine the effect of RES supplementation on liver enzymes and inflammatory markers in patients with nonalcoholic fatty liver disease.	Significant decreases in both groups in circulating and liver inflammatory markers, and ALT levels in response to RES.	Faghihzadeh et al., 2014
7	Patients on statin treatment and at high risk of CVD (n=75).	Three parallel arms, randomized, triple blind, placebo controlled trial.	Follow-up: daily ingestion of 350 mg of 1) placebo (n=25), or 2) grape extract (GE) (n=25), or 3) GE + 8 mg RES, (n=25). Product in capsules.	6 months	Effects on atherogenic markers, i.e. serum lipid profile, Apo B and LDLox.	GE-RES decreased LDL-cholesterol (4.5%); Apo B (9.8%) and LDLox (20%), while GE determined only a significant decrease of LDL-cholesterol (2.9%). No drug interaction was detected.	Tomé-Carneiro et al., 2012a
8	Post-infarction patients (n=40)	Randomized, 2 parallel arms, double-blind, placebo controlled trial..	Follow up: daily ingestion of 10 mg RES (n=20) versus placebo (n=20).. RES in capsules.	3 months	Measure of biomarkers for cardioprotection.	RES decreased LDLcol (8%); improved endothelial function (50%), and left ventricular diastolic function (2%), No effect on inflammatory parameters (CRP and TNF ✔.	Magyar et al., 2012
9	Patients on statin treatment and at high risk of CVD (n=75). (Same cohort as in Tomé-Carneiro *et al*. 2012a).	Three parallel arms, randomized, triple blind, dose-response, placebo-controlled trial.	Follow-up: daily ingestion for 6 months of 350 mg of 1) placebo (n=25), or 2) grape extract (GE) (n=25), or 3) GE + 8 mg RES, (n=25). Further treatment for 6 months with a double dose. Products in capsules.	12 months	Effect on inflammatory and fibrinolytic status of patients.	GE-RES decreased hs CRP (26%), TNF ✔ (-19.8%), PAI-1 (-16.8%) and IL-6/IL-10 ratio (-24%), and increased IL-10 (19.8%). No drug interaction was found.	Tomé-Carneiro et al., 2012b.
10	Patients with stable angina pectoris (n=116).	Randomized, double-blinded, active-controlled.	Follow up: oral supplementation with calcium fructoborate (CF) (112 mg/day), or RES (20 mg/day), or their combination	30 and 60 days	Effect on inflammation biomarkers (hs CRP), left ventricular function markers (N-terminal prohormone of brain natriuretic peptide -	Significant hs CRP decrease in all groups: 39.7% in the CF group; 30.3% in RES plus CF group. The N- terminal prohormone of BNP was	Militaru et al., 2013.

					BNP), and lipid markers (total cholesterol, LDL-c, HDL-c, and triacylglycerols).	significantly lowered by RES (59.7% at 60 d) and by CF (52.6% at 60 d). However, their combination was the most effective and induced a decrease of 65.5%. Lipid markers showed no significant changes from baseline in all groups.	
11	Patients with stable CAD (n=75).	Three parallel arms, randomized, triple-blind, dose response, placebo-controlled trial.	Follow-up: daily ingestion of 350 mg placebo (n=25), grape extract without (GE) (n=25); or with 8 mg RES (GE-RES), n=25) for 6 months, and the double dose for the following 6 months.	12 months	Effect on inflammatory and fibrinolytic status of patients.	Significant increase in adiponectin levels (10%) in GE-RES group in addition to a decrease in PAI-1 levels. Non-HDL colesterol decreased significantly in both GE and GE-RES groups. Downregulation of pro-inflammatory genes expression in PBMCs isolated from GE-RES group patients.	Tomé-Carneiro et al., 2013a.
12	35 adult hypertensive men with a mean age of 60±11 years previously diagnosed with Type 2 diabetes (T2DM).	Three parallel arms, randomized, triple-blind, dose response, placebo-controlled trial.	Daily intake of grape extract vs. RES-supplemented grape extract (8.1 ± 0.5 mg RES per capsule) for 6 months and double dose for the next 6 months.	12 months	To investigate the molecular changes in peripheral mononuclear cells in hypertensive patients with T2DM.	Some cytokines were down-regulated, such as CCL3 and TNF-alfa;. RES modulated the expression of micro RNAs involved in the inflammatory response, including miR663 and miR-30c2.	Tomé-Carneiro et al., 2013b.
13	19 men with a diagnosis of schizofrenia, (18 -65 yrs old), overweight or obese and/or with metabolic disorders.	Randomized, double-blind, controlled trial	The participants received a diet prescription one month before starting the study, then they received placebo or RES (200 mg/day) per 4 weeks	2 months	To determine the efficacy of RES on serum glucose and CVD risk factors	No change in body weight, waist circumference, serum glucose and cholesterol in the RES group. Changes in the lipid	Zortea et al., 2016.

						profile. In the placebo group, there was a significant increase in total cholesterol, LDL-cholesterol and in triglycerides, as well as a reduction in HDL-cholesterol.	
14	Patients with metabolic syndrome (n=34).	Randomized, cross-over, open trial; No control with placebo.	Group A (n=17): Treatment with 100 mg RES in capsules for 3 months followed by 3 months with placebo The inverse pattern in group B, n=17.	6 months	Evaluation of several parameters in patients with metabolic syndrome.	In both groups, Flow-Mediated-Dilatation (FMD) improved from 4% to 10% and returned to baseline values after discontinuation of RES treatment. No effect was observed on other inflammatory and atherogenic biomarkers.	Fujitaka et al., 2011.
15	24 patients previously diagnosed with metabolic syndrome (30 -50 yrs; sex not indicated).	Randomized, double-blinded, placebo-controlled.	Placebo or 500 mg RES 3 times a day, before meals.	90 days	To investigate the effect of RES on insulin release and efficacy in patients with metabolic syndrome.	In the RES group, there were significant reductions in total weight, BMI, fat mass, and weight circumference. There were also significant differences in insulin sensitivity.	Mendez del Villar et al., 2014.
16	Type 2 male diabetic patients (n=19).	Two parallel arms, randomized, double blind, placebo controlled trial.	Daily ingestion of 10 mg RES, n=10 or placebo, n=9. RES in capsules.	4 weeks	Effect on insulin resistance	Decrease of insulin resistance possibly due to a reduction of oxidative stress, as shown by measuring urine and platelet biomarkers	Brasnyó et al., 2011.
17	Type 2 diabetics (n=62).	Randomized trial, placebo- uncontrolled, open, 2 parallel arms.	Daily ingestion of hypoglycemic drugs + 250 mg RES (n=28) or only hypoglycemic drugs in control group (n=29). Products in capsules.	3 months	Effects on glycemic control and associated risk markers.	RES significantly improved concentration of: fasting glycemia (-14.4%); systolic (-11.8%), and diastolic (-2,1%) blood	Bhatt et al., 2012.

						pressures, HbA1c (-0.3%), total colesterol (-14.3%), and LDL-Col (-12.5%); urea-nitrogen (-3.23%9	
18	Overweight/obese and moderately insulin resistant older adults (n=10).	Randomized, placebo-uncontrolled, open-label trial	RES capsules in one of the three doses: 1, 1.5, and 2 g/day	4 weeks	Glucose metabolism and vascular function.	Improved insulin sensitivity and postmeal plasma glycemia. No change in fasting glycemia. No dose-responce.	Crandall et al., 2012.
19	45 patients with diet-controlled type-2 diabetes.	Double-blind, randomized, crossover design	Patients received RES (500 mg twice daily) or placebo over two 5 wks intervention periods with a 5 wks washout, and then cross-over	15 weeks	To evaluate the effects of 5 week of RES treatment on GLP-1 (glucagon-like peptide 1) secretion, gastric emptying, and glycemic control in type-2 diabetes.	No significant change in both groups for any parameter measured.	Thazhath et al., 2016.
20	10 males with Type 2 diabetes mellitus (40-69 yrs old).	Randomized, double-blind, placebo controlled trial.	Subjects were given a starting dose of 500 mg daily of either RES or placebo associated with a RES-free diet The dose was increased by 500 mg/day every 3 days to a maximum dose of 3 g/day. Doses were divided in three administrations.	15 days	To assess the effect of RES on skeletal muscle SIRT1 expression and energy expenditure.	In patients with T2DM, the treatment with RES regulates energy expenditure through increased levels of skeletal muscle SIRT1[6] and AMPK expression. These findings indicate that RES may have beneficial exercise-mimetic effects in patients with T2DM	Goh et al., 2014.
21	Patients with Alzheimer Diseases (n=119).	Two parallel arms, randomized, placebo controlled trial.	Participants received placebo or resveratrol 500 mg orally once daily (with dose escalation by 500-mg increments every 13 weeks, ending with 1,000 mg twice daily).	39 weeks	Penetration of resveratrol and its major metabolites into the blood–brain barrier to have CNS effects.	RES penetrates into cerebral spinal fluid and positively modulates biomarkers of Alzheimer disease. Further in-depth studies are suggested.	Turner et al., 2015.

22	80 post-menopausal women (45–85 yrs).	Randomized, double-blind, placebo-controlled trial.	Two capsules of RES (75 mg/day).	14 weeks	To determine the effects of RES on cognition, cerebrovascular responsiveness to cognitive tasks and overall well-being	According to the results of tests, RES, as other vasoactive nutrients, could enhance mood and cognition and reduce the risk of developing dementia in post-menopausal women and other at-risk populations.	Evans et al., 2016.
23	72 patients with peritoneal dialysis (PD); 8 drop out.	Double-blind, placebo-controlled, and randomized trial.	Patients received placebo (n=24) or trans-RES 150 mg/day (n=22) or 450 mg/day (n=18),	12-weeks	To evaluate effects on angiogenesis-related markers.	Over the 12-week period, patients in the high-dose group showed a significant improvement in mean net Ultrafiltration (UF) volume and UF rate.	Lin et al., 2016.
24	Patients taking an oral contraceptive (n=12 + n=42)..	Unmasked and unrandomized trial.	Two separate experiments: 1) 2 months with 30 mg of RES in addition to oral contraceptive (3 mg drospiredone and 30 ❡ g ethinylestardiol) previously taken for 6 months; 2) Sixteen patients on oral contraceptives alone and 26 with addition of RES for at least 2 months prior to hospital admission.	2 months	Experiment 1: Effect on endometriosis related pain Experiment 2: Effect on aromatase and cyclooxygenase-2 expression in endometrial tissue.	RES significantly reduced pain scores (82% of patients reporting complete resolution of dysmenorrhea and pelvic pain after 2 months of use). Inhibition of both aromatase and cyclo-oxygenase-2 expression was significantly greater in the eutopic endometrium of patients taking RES compared with oral contraceptives alone.	Maia et al., 2012.
25	50 patients with active mild to moderate ulcerative colitis (UC).	Randomized, double-blind, placebo-controlled trial.	Patients received 500-mg RES or placebo.	6 weeks	To evaluate the RES properties as an anti inflammatory and antioxidant agent. Effect on quality of life.	RES significantly reduced plasma levels of TNF-alfa, and activity of NF-kB, in PBMCs.	Samsamikor et al., 2016
26	Eight overweight or obese individuals (28-55 yrs old) with	Randomized, double-blind, placebo-controlled trial.	One g RES daily during 1st week, then 2 g daily during 2nd week.	2 weeks	To evaluate turnover of intestinal and hepatic lipoprotein (ApoB-48	RES decreased production of ApoB-48 and ApoB-100 by 22 and	Dash et al., 2013

	a history of hypertriglyceridemia.				and ApoB-100), whose high levels are markers of aterosclerosis, hearth disease and other CVD.	27%, respectively. No difference in insulin sensitivity, fasting triglycerides, plasma cholesterol, or HDL.	
27	Healthy overweight/ obese men or post-menopausal women with mildly elevated blood pressure (n=19).	Randomized, crossover, double blind, single dose, placebo-controlled trial.	Single ingestion of 30, 90, 270 mg of synthetic RES or placebo at weekly intervals. Analyses were performed 1 h after consumption of the product (capsules).	Three acute doses	Acute, dose dependent effect of RES on Flow Mediated Dilatation (FMD), marker of endotelial function	FMD improved by 65% 1h after consuming 30 or 90 mg RES and by 88% with 270 mg RES.	Wong et al., 2011
28	Healthy adult smokers (n=50).	Randomized, double-blind, placebo-controlled, cross-over trial.	Follow up: patients were allocated to either "resveratrol-first" group (30 days of 500 mg RES/day, 30 days wash-out, 30-days placebo) or to "placebo-first" group (30 days placebo, 30 days wash-out, 30 days 500 mg RES/day).	90 days	Effects on markers of inflammation and oxidative stress in smokers.	Significant CRP and triglyceride concentrations reduction, and increased Total Antioxidant Status values. No significant change in serum uric acid, glucose, insulin, cholesterol, liver enzyme concentrations, and body weight, waist circumference, and blood pressure.	Bo et al., 2012
29	27 aged physically inactive and non-smokers males (60-72 yrs old).	Randomized, double-blind, placebo-controlled trial.	Subjects were allocated to either a combination of exercise training and placebo or exercise training and 250 mg day of trans-RES	8 weeks	To evaluate if RES further enhances training-induced improvements in cardiovascular health parameters in aged men.	The major findings were that 8 weeks of exercise training induced a number of beneficial cardiovascular effects, but parallel supplementation with resveratrol reduced several of these improvements.	Gliemann et al., 2013
30	11 obese “healthy“ men (40-65 yrs old) .	Randomized, double-blind, cross-over trial.	150 mg daily of placebo or RES for 30 consecutive days. 4-week washout period and then cross-over treatment.	90 days	To investigate a 30-day intake of RES on adipose tissue morphology.	RES significantly reduced adipocyte size, which may contribute to the improvement in insulin sensitivity.	Konings et al., 2014
31	10 obese “healthy” men with a mean age	Randomized, double-blind, cross-over trial.	A 4 week washout period was followed by 30 days of RES	2 months	To investigate postprandial incretin	RES had no effect on postprandial incretin	Knop et al., 2013

	of 52±2.		administration (150 mg daily) without other polyphenol consumed.		hormone levels and glucagon responses.	hormone responses, but showed a significant effect in suppressing postprandial glucagon response.	
32	32 overweight "healthy" adults (60-80 yrs old; 16 women). Under no medication.	Randomized, double-blind, placebo-controlled trial.	Daily intake of placebo or 300 or 1000 mg RES, taken in two doses, immediately following breakfast and dinner.	12 weeks	To determine safety and metabolic outcomes of RES supplementation in older adults.	RSV was generally well tolerated. RSV decreased fasting glucose and bilirubin levels.	Anton et al., 2014
33	Nonobese, post-menopausal women (n=45).	Randomized, double-blind, placebo-controlled trial.	75 mg/day of RES	12 weeks	Evaluate the metabolic effects in nonobese, post-menopausal women with normal glucose tolerance.	No change in body composition, resting metabolic rate, plasma lipids, or inflammatory markers. No increase in liver, skeletal muscle, or adipose tissue insulin sensitivity. No effect in RES putative molecular targets, including AMPK, SIRT1, NAMPT, and PPARGC1A, in either skeletal muscle or adipose tissue.	Yoshino et al., 2012
34	Obese "healthy" men (n=24).	Randomized, placebo-controlled, double-blinded, and 2-arms.	Daily intake of three times/day of RES (500 mg) or placebo.	4 weeks	Metabolic effects of RES in obese subjects.	No significant change in insulin sensitivity in both groups. Endogenous glucose production and the turnover and oxidation rates of glucose remained unchanged. No effect on blood pressure, resting energy expenditure, oxidation rates of lipid, ectopic or visceral fat content, or in inflammatory and metabolic biomarkers.	Poulsen et al., 2013.

35	40 healthy post-menopausal women (50-66 yrs old), with an average BMI of 32.9 kg/m^2.	Open trial	Two tablets containing 500 mg RES daily. Restriction in foods containing polyphenols was required two weeks before and during the trial.	12 weeks	To evaluate if RES has a role in systemic sex hormone levels and estrogen metabolites in post-menopausal women to reduce risk factors for breast cancer.	RES intervention did not result in significant changes in sex hormone levels, but did result in a significant increase in sex-hormone binding globulin.	Chow et al., 2014
36	Healthy subjects (n=40).	Open trial, blinded for analysis.	Daily ingestion of 0.5 g (n=10), 1 g (n=10), 2.5 g (n=10) and 5 g (n=10) micronized RES in capsules.	29 days	Evaluation of safety, pharmacokinetics and effects on circulating IGF-1 and IGFBP-3, which are involved in chemioprevention	IGF-1 levels were decreased on the 2.5 g dose and IGFBP-3 on the 1 and 2.5 g doses. No linear dose-response was observed between RES plasma AUC values and effects on IGF-1 and IGFBP-3.	Brown et al., 2010
37	Women at higher breast cancer risk (n=31).	Randomized, 3-arm, double-blind, placebo-controlled trial.	Daily ingestion of placebo, 5 mg or 50 mg RES in capsules.	3 months	Effects on DNA methylation and prostaglandin E2.	No significant effect on the 4 genes studies (RASSF-1 ✔, APC, CCND2 and p16). A correlation was found between the decrease of RASSSF-1 ✔ methylation and serum RES concentration.	Zhu et al., 2012
38	16 healthy male, mean age of 22 years, performing 3 days /week of high intensity training. Unspecified medication, if any.	Randomized, double-blind, placebo-controlled trial.	Daily intake of placebo or 150 mg RES. Subjects were informed to refrain from consuming foods and drinks containing polyphenols for the duration of the study. No nutritional supplement allowed.	4 weeks	To investigate the effects of RES in high-intensity training.	RES did not affect aerobic or anaerobic capacity, or exercise substrate utilization, during training.	Scribbans et al., 2014
39	42 healthy but physically inactive man (60–72 yrs old).	Randomized, double-blind, placebo controlled trial.	Subjects from the first part were assigned to either a combination of exercise training with placebo or exercise training with 250 mg RES/day	8 weeks	To investigate the effects of RES alone and combined with exercise training on metabolic and inflammatory status in skeletal muscle.	Exercise training markedly increased muscle endurance and the content and activity of oxidative proteins as well as decreased the TNFα mRNA content and	Olensen et al., 2014

						protein carbonylation level in skeletal muscle, which are involved in inflammation and oxidative stress. RES did not affect these parameters.	
40	13 healthy, sedentary adults (18-65 yrs old).	Randomized, double-blind, placebo controlled, cross-over trial.	RES and placebo were admistered twice daily. Regarding RES, the dose in the first week, was 500 mg (x2). This was increased to 1000 mg (x2) for the remaining 3 weeks if tolerated by the patient. Then cross-over	4 weeks	To assess the effect of RES on exercise capacity .	RES did not show any significant effect on exercise capacity or any other exercise parameters.	Voduc et al., 2014
41	Obese men (n=11).	Randomized, crossover, double-blind, placebo-controlled trial.	Daily ingestion of 150 mg of synthetic RES in capsules.	1 month	To assess whether RES induces metabolic changes in obese men.	RES induced modest but consistent metabolic changes that mimic caloric restriction, such as reduction of sleeping and resting metabolic rate, activation of AMPK and increase of SIRT1 and PGC-1 in muscle, and others.	Timmers et al., 2011
42	Healthy subjects (n=22).	Randomized, crossover, double-blind, dose-response, placebo-controlled trial.	Single intake of placebo, 250 mg or 500 mg RES in capsules. Analyses were performed 45 min after the ingestion.	Acute dose	Acute effect on brain functions by improving blood flow.	RES increased dose-dependently cerebral blood flow. Cognitive function was not affected.	Kennedy et al., 2010
43	Healthy subjects (n=42).	Open Trial.	Cohort with a single arm to evaluate effects upon daily ingestion of 1 g RES in capsules.	4 weeks	Effect of RES on CYPs and phase II enzymes.	RES inhibited the activity of CYP3A4, CYP2D6, and CYP2C9 and induced CYP1A2, with possible effect on drug metabolism.	Chow et al., 2010
44	74 middle aged obese men (41.8-	Randomized, double-blind, placebo-	Placebo or intake of 500 mg/day, or 75 mg twice daily.	16 weeks.	To evaluate the effects of RES on bone	Bone density increased in a dose-dependent manner	Ornstrup et al., 2014

	56.8 yrs old), with metabolic syndrome.	controlled trial.	Participants were instructed to avoid nutritional supplements during the study		turnover markers, bone mass and structure.	by stimulating bone mineralization.	
45	10 healthy male volunteers (21–28 yrs old).	Randomized open trial.	One single 5 g dose of RES. Subjects received a standard diet not containing polyphenols during the study period.	48 hours	To determine the effect of RES on human mononuclear cells upon bacterial stimulation.	RES-treated individuals showed an increase in TNF-✔ levels after a 24-h treatment while IL-10 levels decreased. In this study, RES shows anti-inflammatory and immunomodulant properties.	Gualdoni et al., 2014

Table 3 – Summary of resveratrol's effects in humans with different diseases

Area	**No. of studies (Ref. to Table 1)**	**Daily dose range (Lowest active dose)**	**Comments**
Cancer	3 (1-3)	0.07-5 g (0.07 g)	Positive effects on markers of cellular proliferation, migration and apoptosis.
Fatty liver	3 (4-6)	0.3 -3 g (0.3 g)	Reduction of hepatic enzymes and opposing results on inflammatory markers.
CVD	7 (7-12)	0.5-200 mg (0.5 mg)	In most studies, reduction of LDL-cholesterol (≥8 mg) and some inflammatory markers (≥0.5 mg).
Metabolic syndrome	3 (13-15)	0.1-1.5 g (1.5 g)	No significant effects on flow mediated dilatation till 0.1 g/day. Positive modulation of metabolic syndrome parameters at 1.5 g/day.
Diabetes	5 (16-20)	0.01-3 g (0.01 g)	Most studies showed improvement of insuline sensitivity; contradictory results in reduction of glycemia.
Cognitive functions	2 (21-22)	0.075-2 g (0.075 g)	General improvement of cognitive fuctions requiring further research to be confirmed.
Other	3 (23-25)	0.03-0.5 g	Reduction of pain score in women with dysmenorrhea (30 mg/day) and improvement of inflammatory biomarkers in ulcerative colitis (500 mg/day). Improvement in mean net ultrafitration volume and rate in dialized patients (≥450 mg/day).

Table 4 – Summary of resveratrol's effects in healthy humans

Area	**N.of studies (Ref. to Table 1)**	**Daily dose range (Lowest active dose)**	**Comments**
Cardiovascular	4 (26-29)	0.030-2 g (0.030 for endotelial function)	Decreased levels of risk factors for CVD: ApoB48 and ApoB100, endotelial function and oxidative stress, etc.
Insulin sensitivity	5 (30-34)	0.075-1 g	No significant result on glycemia and insulin sensitivity.
Chemioprevention	3 (35-37)	0.005-5 g	No significant effect.
Training performance	4 (38-41)	0.15-2 g	No effects on training performance.
Cognitive function	1 (42)	0.250-0.5 (0.25)	No effect on cognitive function, improvement in cerebral blood flow.
Hepatic metabolic function	1 (43)	1 g	Possible effect (positive or negative) on hepatic metabolism of drug.
Bone mineralization	1 (44)	0.15-0.5 g	Dose-response improvement of bone density.
Immunomodulation	1 (45)	5 g	Improvement of immunomodulation and inflammation.

Figure Legends

Figure 1. Oxidative stress snowball effect. Stages on redox homeostasis evolution in time. In (y) redox homeostasis in (x) years

Figure 2. Evolution of oxidative stress in time. 1) cellular breathing oxidative status average; 2) oxidative stress by physiological stimulation (e.g. postprandial); 3) and 4) acute to mild chronic oxidative stress; 5) acute to moderate chronic oxidative stress; 6) acute to severe chronic oxidative stress (Modified from Preiser, 2012).