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Anti-oxidative action of resveratrol: Implications for human health

Kanti Bhooshan Pandey, Syed Ibrahim Rizvi *

Department of Biochemistry, University of Allahabad, Allahabad 211002, India

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Abstract Resveratrol, the red-wine polyphenol, is intensively studied polyphenols for its pleiotropic biological effects. A plethora of health beneficial effects of this stilbene has been reported including cardio-protective, neuro-protective, anti-cancer, anti-diabetic and interesting anti-aging. Though it has been proposed that these effects of resveratrol arise from its capacity to interact with multiple molecular targets involved in diverse intracellular pathways including activation of sirtuins, the antioxidant property of this compound is the most described one to attribute its diverse health beneficial effects. In the present review we have explained the biological activities of resveratrol with the latest laboratory evidences towards its antioxidant effects.

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1. Introduction

Herbal medicines have been used for thousand years to fight diseases and improve body functions. Polyphenols present in these herbal remedies are considered as major nutrients responsible for improving general health and for providing cure for certain specific pathological conditions (Pandey and Rizvi, 2009a). Resveratrol is a naturally occurring polypheno-

lic compound found largely in the skins of the grapes (*Vitis vinifera*) and the products prepared from it such as red-wine, however presence of resveratrol has been identified in several other plant species except grapes such as peanuts, berries and legumes (Aggarwal et al., 2004). Its stilbene-based structure has two phenolic rings linked by a styrene double bond, which allows *cis* and *trans* orientation to generate 3,4',5-trihydroxystilbene (Fig. 1) (Markus and Morris, 2008).

Resveratrol has a long history of serving mankind as part of several herbal medicinal preparations all over the world. Roots of *Polygonum cuspidatum*, a plant used in traditional Chinese and Japanese folk medicine has been found to be rich in resveratrol. The primary impetus for research on resveratrol came from the paradoxical observation of a low incidence of cardio-vascular diseases that coexist with intake of a high-fat diet and moderate consumption of red-wine in certain populations, a phenomenon known as French paradox (Renaud and de Lorgeril, 1992; Siemann and Creasy, 1992).

Several studies within the last few years have demonstrated that resveratrol may prevent or slow the progression of a wide variety of human diseases, including cancer, cardio-vascular

* Corresponding author. Tel.: +91 945015305910.
E-mail address: sirizvi@gmail.com (S.I. Rizvi).



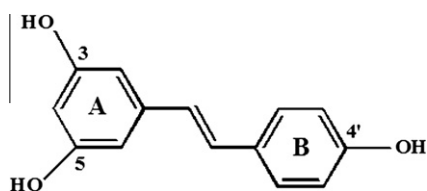


Figure 1 Chemical structure of resveratrol.

diseases (CVDs) and ischemic injuries as well as to enhance stress resistance and extend the life-spans of a variety of organisms from yeast to vertebrates (Fig. 2) (Jang et al., 1997; Markus and Morris, 2008; Pandey and Rizvi, 2009b). Activation of sirtuins, a class of nicotinamide adenine dinucleotide (NAD⁺)-dependent deacetylases, modulation of cell cycle regulatory genes, activation of transcription factors and inhibition of protein kinases are some proposed mechanisms of action of resveratrol (Marques et al., 2009), however, the anti-oxidative property is one of the most documented biological activity of resveratrol for its diverse biological effects. The aim of the present review is to highlight the latest findings that are responsible for the increased recognition of resveratrol as a potent antioxidant agent.

2. Reactive oxygen species and oxidative stress

Reactive oxygen species (ROS) is a collective term that includes oxygen-centered radicals and oxygen-centered non radicals that are continuously produced as a byproduct during normal metabolic processes inside the human body. Exogenous factors such as UV exposure, herbicides, xenobiotics and air pollutants also cause the generation of ROS. ROS elicit negative effects on the biomolecules and alter/modulate the normal function of the cell. ROS have been also known to induce proliferation, senescence, necrosis, apoptosis or cell death (Simon et al., 2000).

To overcome the deleterious effects of ROS, antioxidant systems are inherently present in human body. However due to over generation of ROS/weak defense systems, an imbal-

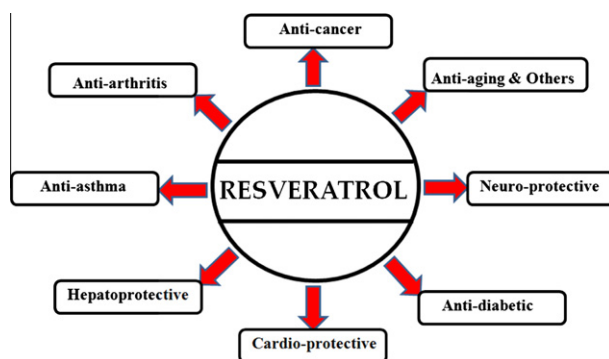


Figure 2 Diverse health beneficial effects of resveratrol. Anti-cancer and cardio-protective effects are first reported biological effects of resveratrol. Prolongation of life span in lower vertebrates and protective effects in many age related diseases are some evidences to establish resveratrol as anti-aging agent. However anti-diabetic, analgesic, anti-arthritis, anti-asthma and immunity enhancement effects are some currently reported biological effects of resveratrol.

ance occurs between this redox system and the condition of oxidative stress develops. Oxidative stress is always deleterious and it causes damage to tissues in many ways (Sies, 1986; Halliwell, 2007).

Oxidative stress changes the ion balance that triggers many other deleterious events such as cellular volume changes (Schliess and Häussinger, 2002). Oxidative stress causes damage to a wide range of biomolecules including proteins, lipids and nucleic acids, making them oxidized and malfunctioned. In clinical studies oxidative stress has been associated with many degenerative diseases such as atherosclerosis, cancer, trauma, stroke, asthma, hyperoxia, arthritis, age pigments, dermatitis, cataractogenesis, retinal damage, hepatitis and aging (Halliwell and Gutteridge, 2006; Pandey and Rizvi, 2010b).

3. Resveratrol as a potent antioxidant

Resveratrol is reported to one of the most potent antioxidant against ROS and oxidative stress. ROS production by polymorphonuclear leukocytes stimulated by formylmethionyl leucyl phenylalanine (fMLP) can be strongly inhibited by resveratrol (Rotondo et al., 1998). Mizutani and co-workers (2001) showed that resveratrol significantly reduces markers of oxidative stress like glycated albumin in serum and 8-hydroxyguanosine in urine in stroke-prone spontaneously hypersensitive rats. Moreover, resveratrol could act on targets in blood cells and in lipoproteins. Indeed, resveratrol was incorporated into blood cells and lipoproteins after *in vitro* incubation with plasma, lipoproteins, and cells (Blache et al., 1997). In fact, due to its lipophilic character, resveratrol is able to bind the lipoprotein particles suggesting that this event improved its antioxidant activity (Belguendouz et al., 1998). Here we will discuss the effect of resveratrol on some most reliable and authentic parameters of oxidative stress to explain the extent of anti-oxidative effects of resveratrol.

3.1. Resveratrol and lipid peroxidation

Lipids are the important constituents of membranes and function as steroid hormones, retinoic acids and prostaglandins. In view of increasing evidence showing the involvement of free radicals in biology, lipid peroxidation has received renewed attention from wider viewpoints in the fields of chemistry, biochemistry, nutrition, and medicine. Studies have revealed that lipid peroxidation severely affects biomembranes including disturbance in fine structures, alteration of integrity, fluidity, permeability and functional loss and also modifies low density lipoprotein (LDL) to pro-atherogenic and pro-inflammatory forms, and generates potentially toxic products (Greenberg et al., 2008). Lipid peroxidation products have also been shown to be mutagenic and carcinogenic (West and Marnett, 2006) and has been implicated as the underlying mechanisms in numerous disorders and diseases such as cardio-vascular diseases, cancer, neurological disorders, and also in aging (Lee et al., 2004; Rizvi and Maurya, 2007).

A measurable increase in plasma antioxidant level and decreased lipid peroxidation has been seen after consumption of resveratrol or resveratrol-rich diet (Wenzel et al., 2005). An association has been found between oxidation of LDL particles and risk of heart diseases and myocardial infarctions

(Markus and Morris, 2008). Resveratrol prevents oxidation of LDL by chelating copper and by scavenging ROS. The fact that resveratrol can be detected in LDL particles after red-wine consumption by humans is consistent with its ability to prevent peroxidation of lipids and other macromolecules (Markus and Morris, 2008).

The efficiency and action mechanism of *trans*-resveratrol have been demonstrated in the radical liposome oxidation where it appeared that the *para*-hydroxyl groups show a greater radical-scavenging activity than the *meta*-hydroxyl groups of *trans*-resveratrol (Stojanovic et al., 2001). Moreover, the spatial position of hydroxyl groups is likely more propitious to the chelation of copper in the *trans*-isomer than in the *cis*-isomer. It has been reported that due to hydroxylated structure of resveratrol, it can form a radical derivative stabilized by the delocalization of two electrons between the two aromatic cycles and the methylene bridge joining these two cycles (Delmas et al., 2005).

Resveratrol is also reported to reduce the intracellular ROS and to prevent the LDL oxidation in endothelial cells (Delmas et al., 2005). Oxidation induced by endothelial cells depends on lipoperoxides generated intracellularly and then transferred to the LDL. Cellular lipoxygenases (LO), especially 15-LO, appear to be involved. Various studies demonstrate that resveratrol inhibits lipoxygenases, in particular in human neutrophils where resveratrol strongly inhibits the 5-LO and 15-LO producing various pro-inflammatory products in the arachidonate metabolism (MacCarrone et al., 1999). In addition resveratrol was able to decrease the accumulation of hydroperoxides in LDL promoted by ferromyoglobin by reduction of the oxoferyl complex to metmyoglobin. Resveratrol also inhibited LDL apoprotein modifications induced by peroxynitrite (Brito et al., 2002).

In 2008, Dani and co-workers showed that resveratrol has ability to prevent lipid peroxidation and intracellular oxidation in *Saccharomyces cerevisiae*. They have reported that after resveratrol treatment, the levels of ROS produced in *Saccharomyces* in response to peroxide were almost 3-fold lower, suggesting that resveratrol has a high capacity to eliminate hydroxyl radicals formed by a Fenton reaction.

One of the most often used biomarker to investigate the oxidative damage on lipids is malondialdehyde (MDA), a major lipid peroxidation product. It can react with the free amino group of proteins, phospholipids, and nucleic acids leading to structural modification, which can induce dysfunction of immune systems. A high level of MDA can be detected in cell degradation after cell injury or disease (Pandey et al., 2009a,b). A very recent study done in our lab showed that the presence of resveratrol in incubation media very effectively protected the erythrocyte lipids from peroxidation as evidenced by the almost normal (control) values of the MDA in cells even after induction of oxidative stress (Pandey and Rizvi, 2009c). In 2003, Leonard and co-workers have reported that that resveratrol can scavenge ROS as measured by spin trapping competitions using sodium formate as a second free radical scavenger, and is effective in inhibiting lipid peroxidation of cellular membranes. Ray et al. (1999) have reported that MDA formation in the coronary effluents of the resveratrol-treated hearts was significantly lower than those of control animals, suggesting reduced free radical formation in the hearts pretreated with resveratrol. Protective role of resveratrol in MDA formation in naphthalene-induced oxidative stressed

mice is also reported (Sehirli et al., 2008). Moreover, intraperitoneal resveratrol administration has been shown to reduce lipid peroxidation and tissue damage in ischemia/reperfusion (Shigematsu et al., 2003) and cholestasis models (Ara et al., 2005). In an *in vitro* study examining the antioxidant activities of resveratrol and its analogues, the results exhibited that they had various potencies in inhibiting lipid peroxidation in rat brain, kidney and liver homogenates and rat erythrocyte hemolysis (Lu et al., 2002).

Interestingly, the effect of resveratrol on protection of lipids from peroxidation is quite fast, within half an hour it showed the significant protection (Pandey and Rizvi, 2009c). Time dependent effect of resveratrol may be explained from the findings of Bertelli et al. (1996) and Goldberg et al. (2003), in which they have documented that resveratrol was rapidly absorbed and its peak plasma concentration was achieved after only 15–60 min of administration. Results from these studies show that resveratrol has strong antioxidant property and also has ability to provide protection against oxidation induced damage to lipids under conditions that challenge the body's redox status.

3.2. Resveratrol and oxidation of proteins

Resveratrol has also been reported for its strong role in protecting the proteins from being oxidized. Resveratrol protected formation of membrane protein carbonyls (PCO) in red blood cells and plasma under the condition of oxidative stress (Pandey and Rizvi, 2009c, 2010a).

The attack by ROS against proteins modifies amino acid (lysine, arginine, proline, and histidine) residues generating carbonyl moieties, which has been identified as an early marker for protein oxidation and is used as a measure of protein damage (Levine et al., 1990). Increase in protein carbonyls level is direct evidence towards the fact that oxidative stress increases as the antioxidant capacity of the body falls (Stadtman, 2001).

Oxidative damage has been reported to occur on all components of biological systems however, proteins are likely to be major targets of ROS due to their abundance in cells, plasma, and most tissues, and their rapid rates of reaction both with many radicals and with other oxidants. It has been reported that proteins compose about 70% of the dry mass of most cells (Hawkins et al., 2009). Since proteins often have unique biological functions, there are unique functional consequences resulting from their modification. Oxidation of proteins can lead to a whole variety of amino acid modifications. Action of chloraminated oxidants, mainly hypochlorous acid and chloramines, produced by myeloperoxidase in activated neutrophils, forms dityrosine containing cross-linked protein products known as advanced oxidation protein products (AOPP) (Witko-Sarsat et al., 1996). Protein oxidation products mediated by chlorinated species generated by an enzyme myeloperoxidase were found in the extracellular matrix of human atherosclerotic plaques and increased levels of AOPP were described as an independent risk factor for coronary artery and renal diseases (Witko-Sarsat et al., 1996). Inhibition of formation of AOPP and PCO by resveratrol directly advocates its strong antioxidant effect (Pandey and Rizvi, 2010a).

Resveratrol has also been consistently shown to inhibit protein degradation and to attenuate atrophy of skeletal muscle fibers *in vitro* (Dirks Naylor, 2009). In 2007, Busquets et al.

reported that incubation of the isolated rat extensor digitorum longus muscle in resveratrol significantly reduced protein degradation compared to control muscle. It appears that resveratrol may inhibit protein degradation by inhibiting the activation and translocation of nuclear factor kappa beta (NF- κ B) to the nucleus (Dirks Naylor, 2009). Resveratrol may inhibit activation of NF- κ B via the inhibition of I- κ B kinase (IKK) (Holmes-McNary and Baldwin, 2000).

It has been reported that resveratrol supplementation (1 mg/kg/day) in MAC 16 tumor bearing rats did significantly attenuate weight loss and protein degradation in skeletal muscle as well as reduce the NF- κ B activity (Wyke et al., 2004). In 2006, Ikizler et al., reported that resveratrol has excellent antioxidant activity. It protected skeletal muscles from oxidative stress and injury as determined by carbonyl and protein sulphhydryl levels as well as venous levels of myoglobin, lactate dehydrogenase, creatinine phosphokinase. Dirks Naylor, 2009 has been concluded that in skeletal muscle, resveratrol has thus far been shown to alter metabolism, inhibit protein catabolism, improve function, and protect against cellular stress.

3.3. Resveratrol and endogenous antioxidant systems

To overcome deleterious effects of ROS, many antioxidant systems are inherently present in human body. In humans, the antioxidant system includes a number of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT), non-enzymatic antioxidants such as reduced glutathione (GSH), protein -SH and uric acid. It has been elaborated that resveratrol significantly activates/ prevents the oxidation of these endogenous antioxidant systems.

Resveratrol is able to induce cellular antioxidants and phase 2 enzymes (Marques et al., 2009). These modifications contribute to increase the resistance to cardiac cell injury elicited by ROS. It has been found that resveratrol reduces the generation of H_2O_2 , and normalize levels of oxidized glutathione reductase and myeloperoxidase activities (Jang and Pezzuto, 1999). By normalization of the ROS levels, resveratrol limits the oxidative stress which inhibits NO synthesis by eNOS necessary for vasorelaxation (Delmas et al., 2005).

GSH is a major intracellular non-protein sulphhydryl compound and is accepted as the most important intracellular hydrophilic antioxidant (Melov, 2002). GSH has many biological functions, including maintenance of membrane protein -SH groups in the reduced form, the oxidation of which can otherwise cause altered cellular structure and function. It plays a key role in protecting cells against electrophiles and free radicals. This is due to the nucleophilicity of the -SH group and to the high reaction rate of thiols with free radicals (Manson, 1979). Stress resistance of many cells is associated with high intracellular levels of GSH. A decreased GSH content may predispose the cell to a lower defense against condition of oxidative stress during several degenerative disease conditions including aging and diabetes (Rizvi and Zaid, 2001; Rizvi and Maurya, 2007).

In 2003, Yen et al. showed that resveratrol at concentrations of 10–100 μ M exerts great protection against H_2O_2 induced oxidative injury through increased GSH levels. Another study by Ates et al. (2007) confirms that an elevation in glutathione level is due to the free-radical scavenging prop-

erties of resveratrol. In a time dependent study of capacity of resveratrol to prevent oxidation of GSH in red blood cells, it is found that resveratrol was very effective since only after 15 min of incubation (Pandey and Rizvi, 2010c).

In 2008, Sehirli et al. reported that naphthalene administration significantly reduced the total antioxidant capacity of plasma with a concomitant decrease in tissue antioxidant, GSH levels. Furthermore, resveratrol treatment replenishes the antioxidant status of plasma and the tissue and protected against this toxicity (Fig. 3).

Resveratrol also showed very significant protection of erythrocyte membrane as well plasma total -SH groups from the oxidizing effects of oxidative stress. In our study on the human blood resveratrol protected the depletion of total -SH groups in concentration as well as time dependent manner (Pandey and Rizvi, 2010c). The importance of -SH group to overall cellular redox balance has been well emphasized. Membrane oxidative damage has a great influence upon the membrane mechanical properties. A reduced level of -SH content has been reported in many human diseases including diabetes and aging (Rizvi and Maurya, 2007; Pandey et al., 2009c).

Endogenous antioxidant enzymes are powerful means to protect the body from adverse modifications of oxidative stress and maintaining the redox balance. SOD catalyzes the dismutation of superoxide radical to H_2O_2 . Although H_2O_2 is not a radical, it is rapidly converted by fenton reaction into $\cdot$ OH radical which is very reactive. CAT metabolizes H_2O_2 into H_2O , it has been reported that oxidative stress is the primary factor regulating the gene expression of these enzymes (Franco et al., 1999). There are many experimental evidences that resveratrol induces the activity of these antioxidant enzymes. In a study by Cao and Li (2004) investigating the mechanism underlying the protective effects of resveratrol in various cardiovascular disorders, it has been demonstrated that a number of endogenous antioxidants and phase 2 enzymes, including SOD, CAT, glutathione reductase (GR), glutathione S-transferase (GST), and NAD(P) H:quinone oxidoreductase 1 (NQO1) in cultured cardiomyocytes can be induced by low

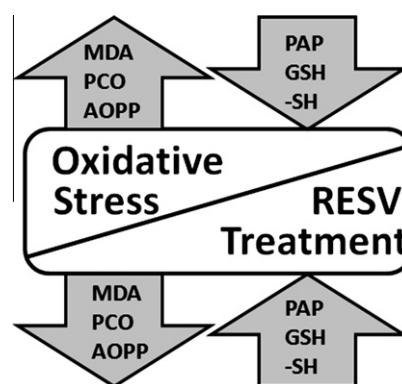


Figure 3 Diagrammatic representation of relation between oxidative stress parameters and effect of resveratrol (RESV) treatment. In oxidative stress condition reduced/depletive level of plasma antioxidant potential (PAP), reduced glutathione (GSH) and total thiols (-SH) are reported. In contrast the level of malondialdehyde (MDA), protein carbonyls (PCO) and advanced oxidation protein products (AOPP) are elevated. Resveratrol treatment reversed these conditions of oxidative stress.

micromolar concentrations of resveratrol and that this chemically mediated up-regulation of cellular defenses is accompanied by a markedly increased resistance to cardiac cell injury elicited by ROS, and doxorubicin.

A study carried out by Upadhyay et al., in 2008, elaborates that resveratrol shows a protective activity against hepatic toxicity as evidenced by its ability to modulate pyrogallol-induced changes in hepatic toxicity markers, xenobiotic metabolizing enzymes and oxidative stress. A recent study by Khan et al., 2010, also provides evidence towards anti-oxidative enzyme activating potential of resveratrol as evidenced by the up-regulation of activities of glutathione peroxidase (GPx), GR, CAT and SOD by resveratrol in 6-hydroxydopamine-induced oxidative damage and dopamine depletion in rat model of Parkinson's disease.

4. Conclusion

In summary, present review provides enough evidence for the potential of resveratrol to establish it as a strong antioxidant which may provide effective protection against oxidative stress implicated in the etiology and progression of several acute and chronic diseases. However questions like bioavailability and concentration to be used are still unanswered. The results from clinical trials specially in humans are limited, further research and more clinical studies are necessary in order to ensure efficacy of resveratrol as a dietary antioxidant to be used as supplement.

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