

# Resveratrol: Antioxidant-Pro-Oxidant

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**Abstract-**Resveratrol is a natural polyphenol that presents various physiological activities. Resveratrol mainly found in many kinds of plants and their derivatives. Studies have reported that the methylated derivatives of resveratrol show better potential antifungal and anti-proliferative activities than resveratrol. The present review focuses on its physiological activities, such as cancer chemopreventive activity and protective effect on cardiovascular system. It has been reported that the regular consumption of red wine which contain a resveratrol in a sufficient quantity may in part account for the apparent compatibility of a high fat diet with a low incidence of heart diseases.

In the current review, we also focus on the antioxidant and pro-oxidant properties of resveratrol and also the role of RNS generation. All of the observed effects of resveratrol, including induction of apoptosis at its higher concentration, are also compatible with its putative chemopreventive and antitumor activity.

**Keywords:** Resveratrol, Polyphenol, Chemopreventive activity, RNS, Antioxidant activity.

## 1. INTRODUCTION

Resveratrol (3, 4', 5-trihydroxystilbene) is a phytoalexin found in a wide variety of dietary sources including grapes, plums and peanuts. It is also present in wines, especially red wines and to a much lesser extent in white wines. Its stilbene structure is related to the synthetic oestrogen diethylstilbestrol. Resveratrol exists as cis- and trans-isomers. Trans-resveratrol is the preferred steric form and is relatively stable if it will be protected from high pH and light. The synthesis of trans-resveratrol in the plants could be induced by microbial infections, UV radiation and exposure to ozone (Ignatowicz E. et al., 2001; Soleas G.J. et al., 2001; Pervaiz S., 2003). A primary impetus for research on resveratrol was initiated from the paradoxical observation. A low incidence of cardiovascular diseases may co-exist with a high-fat diet intake and moderate consumption of red wine (Renaud S.C et al., 1992; Soleas G.J et al., 1997), a phenomenon known as the French paradox (Ignatowicz E. et al., 2001). The possible mechanisms by which resveratrol exerts its cardio- and vascular-protection involve inhibition of platelet aggregation, arterial vasodilation mediated by NO (nitric oxide) release, favourable changes in lipid metabolism such as LDL (low-density lipoprotein)- cholesterol oxidation, antioxidant effects, stimulation of angiogenesis (Maulik. N., 2006), induction of cardioprotective protein expression, and insulin sensitization. Indeed, it reduces the synthesis of certain lipids and eicosanoids that tend to promote inflammation and atherosclerosis; likewise, it suppresses certain cardiac arrhythmias (Providencia R., 2006). Some of these effects may be due in part to resveratrol being a phytoestrogen, i.e. a plant compound that has biologically similar properties to those of oestrogens (Delmas D. et al., 2005).

More recent results provide interesting insights into the effect of this compound on the lifespan of yeasts and flies, implicating its potential as an anti-aging agent in treating age-related human diseases (Lastra C. et al., 2005; Holme A.L et al., 2007).

Additionally, some investigators have indicated a potential neuroprotective activity for resveratrol based on its beneficial effects in several brain damage models. Similarly, several studies have identified resveratrol as the beneficial agent in the control of inflammatory disorders such as arthritis and inflammatory bowel disease (Martin A.R et al., 2004; Martin A.R. et al., 2006). Potential mechanisms implicated include: inhibition of synthesis and release of pro-inflammatory mediators, modification of eicosanoid synthesis, inhibition of activate immune cells and inflammatory enzymes such as iNOS (inducible NOS (nitric oxide synthase)) and COX-2 (cyclo-oxygenase-2) through its inhibitory effects on NF-κB (nuclear factor κB) or the AP-1 (activator protein-1) signalling pathways (Lastra C. et al., 2005). One of the most striking biological activities of resveratrol intensely investigated during the last years has been its cancer chemo-preventive or anticancer properties. These properties were first appreciated when Jang et al.,(1997) demonstrated that resveratrol possesses cancer-chemopreventive and cytostatic properties via the three major stages of carcinogenesis, i.e.initiation, promotion and progression (Aziz M.H. et.al 2003). Since then, there has been a flurry of papers reporting the implication of resveratrol in cancer chemoprevention through a broad range of actions that are still poorly understood. It appears to help detoxify carcinogens, synthesis of various cancer-related compounds and interfere with cell survival programmes. Resveratrol has been shown to promote

apoptosis in cancer cells by blocking anti-apoptotic proteins expression or by inhibiting signal transduction through the PI3K (phosphoinositide 3-kinase), MAPK (mitogen-activated protein kinase) or NF- $\kappa$ B pathways (Pervaiz, S., 2003; Holme, A.L. et al., 2007; Fulda, S et al., 2006).

Most of the scientific evidence for resveratrol's benefits are based on in vitro studies in which the diastereomers Trans- or cis-resveratrol have been tested. However, from animal studies and human trials, we know that the predominant isomer that is orally ingested with foods is trans-resveratrol glucoside that is bio transformed and rapidly eliminated. Also, these derivatives might be less biologically active due to their esterified hydroxyl groups. However, the chemo preventive activity of orally administered trans-resveratrol has almost been demonstrated in cancer-induced animal models (Somoza V., 2005). Nonetheless, future studies are needed to know the effective dose required to achieve the health benefits evidenced in experimental models.

## 2. RESVERATROL AS FREE RADICAL SCAVENGER AND ANTIOXIDANT

Over the last few years, many studies have provided evidence for an important role of ROS (reactive oxygen species) in mediating the development of oxidative stress. Excessive ROS accumulation may induce the oxidative modification of cellular macromolecules (lipid, proteins and nucleic acids) with deleterious potential. In fact, DNA damage by ROS has been implicated in mutagenesis, oncogenesis and ageing. Oxidative lesions in DNA include base modifications, sugar damage, strand breaks and basic sites (Ahmad A. et al., 2005). Since gene transcription can be regulated by oxidants, antioxidants and other determinants of the intracellular redox state, ROS can also produce protein damage, inducing other types of mutations. One of the biological activities that have ascribed to resveratrol involves its antioxidant potential. Resveratrol is both a free radical scavenger and a potent antioxidant because of its ability to promote the activities of a variety of antioxidant enzymes (Figure I). The ability of the polyphenolic compounds to act as antioxidants depends on the redox properties of their phenolic hydroxy groups and the potential for electron delocalization across the chemical structure (Lastra C. et al., 2006).

The recognition of resveratrol as a natural antioxidant was clarified by Zini et al. (1999). They suggested three different antioxidant mechanisms: (i) competition with coenzyme Q and, to decrease the oxidative chain complex, the site of ROS generation, (ii) scavenging  $O_2^-$  radicals formed in the mitochondria and (iii) inhibition of LP (lipid peroxidation) induced by Fenton reaction products. In fact, numerous studies have demonstrated the ability of resveratrol to scavenge both  $O_2^-$  and  $OH^-$  radicals (Leonard S. et al., 2003; Losa, G.A., 2003; Moreno J.J et al., 2000). By contrast, in a study (Orallo et al., 2002), using the enzymatic hypoxanthine oxidase-XO (xanthine oxidase) system, resveratrol neither affected the XO activity nor scavenged  $O_2^-$  radicals in rat macrophage extracts. All cells possess numerous defence mechanisms that include enzymes such as SOD (superoxide dismutase), catalase, glutathione reductase and glutathione peroxidase to protect tissues against the deleterious effects of ROS.

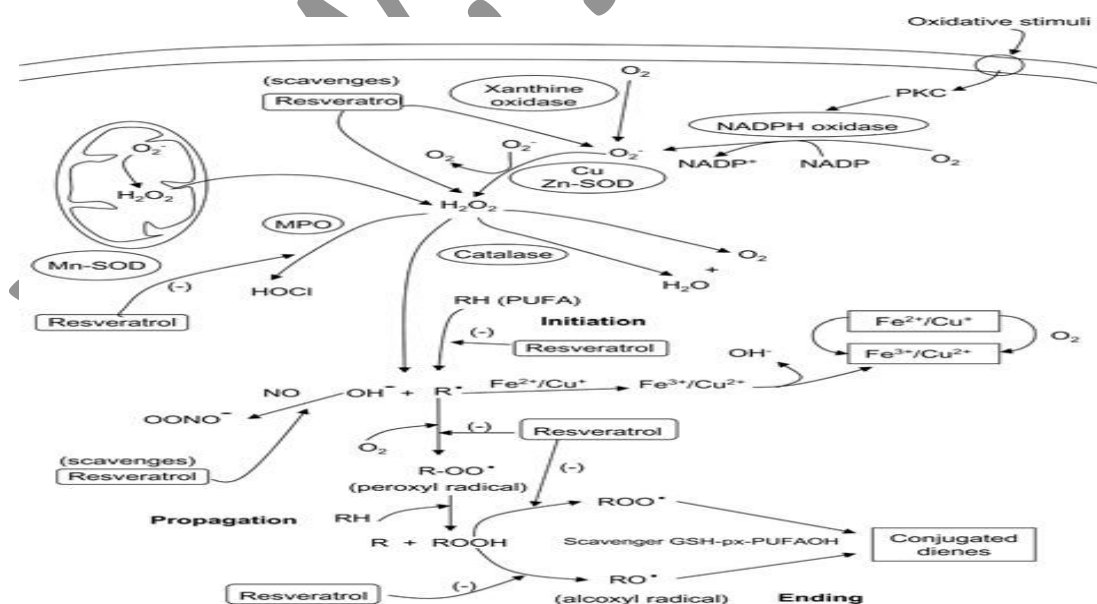


Fig. 2.1 Resveratrol Antioxidant Potential

Resveratrol can maintain the concentration of intracellular antioxidants found in biological systems. For instance, in a study by Losa (2003), stilbene appeared to maintain the glutathione content in peripheral blood mononuclear cells

isolated *ex vivo* from a healthy human from oxidative damage caused by 2-deoxy-D-ribose. In a previous study, in human blood platelets, resveratrol markedly decreased oxidation of thiol groups of proteins in these cells (Olas B. et al., 2004). Similarly, resveratrol induced an increase in glutathione levels in a concentration dependent manner in human lymphocytes activated with  $H_2O_2$ . In another study, resveratrol increased the amounts of several antioxidant enzymes, including glutathione peroxidase, glutathione S-transferases and glutathione reductases (Yen G.C et al., 2003).

### 3. EFFECTS OF RESVERATROL ON RNS (REACTIVE NITROGEN SPECIES) GENERATION

It is now widely accepted that a moderate concentration of NO appears to play cardio- and neuro-protective effects. Reports also have indicated the role of resveratrol in the regulation of NO production from vascular endothelium in the ischemic heart, brain and kidney (Hung L.M. et al., 2000, and Hattori. R. et al., 2002). However, abnormally high concentrations of NO and its derivatives RNS have been associated with tumour growth and vascular invasion. In a previous study (Lorenz P. et al., 2003 ), the effects of resveratrol and oxy-resveratrol on nitrosative and oxidative stress derived from microglial cells were investigated. Phytoalexin considerably diminished NO production upon the inducible isoform of NOS (iNOS expression), and it also induced an inhibitory effect on the iNOS enzyme activity. Bacterial endotoxin LPS (lipopolysaccharide) is one of the most important stimuli for iNOS induction, resulting in NO production that has bactericidal effects. For example, in LPS activated RAW 264.7 macrophages, pre-incubation of cells with resveratrol reduced inflammation by down-regulation of the iNOS and mRNA (Tsai S.H. et al., 1999, Wadsworth T. L. et al., 1999). The results obtained demonstrate that resveratrol is a potent inhibitor of the antipathogen responses of rat macrophages and thus suggest that this agent may have applications in the treatment of diseases involving macrophage hyper-responsiveness (Matsuda H. et al., 2000; Leiro J. et al., 2002).

### 4. ANTIOXIDANT ACTIVITY OF RESVERATROL AND CARCINOGENESIS

Resveratrol prevents the initial DNA damage by two different pathways first by acting as an antimutagen through the induction of Phase II enzymes, such as quinone reductase, capable of metabolically detoxifying carcinogens by inhibiting COX and cytochrome P450. Second by acting as an antioxidant through inhibition of DNA damage by ROS (Roemer K. et al., 2002). It has proposed that ROS derived from LP may function as tumour initiators (Leonard et al., 2003). Leonard et al., 2003 have also shown that resveratrol exhibits a protective effect against LP in cell membranes and DNA damage caused by ROS.

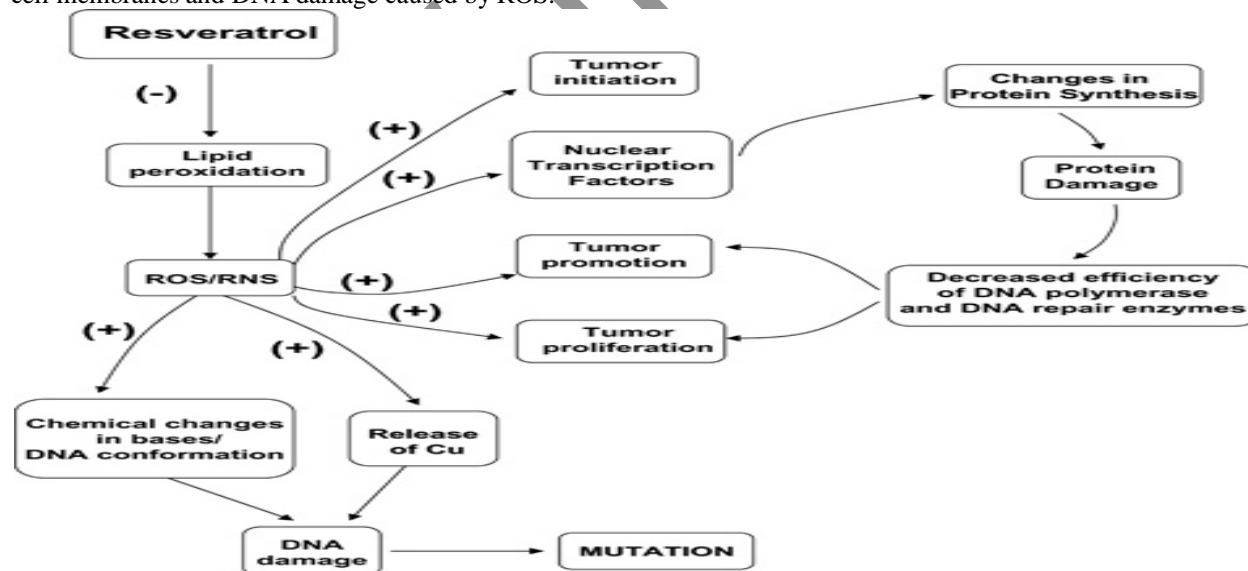


Fig. 4.1 Inhibition of LP by Resveratrol and its Antioxidant Mechanisms in Carcinogenesis

The anti-promotional properties of resveratrol can be partly attributed to its ability to enhance gap-junctional intercellular communications in cells exposed to tumour promoters such as PMA (Gusman J. et al., 2001). The tumour-promoting activity mediated by PMA has also associated with oxidative stress by increased production of  $O_2^-$  and  $H_2O_2$ , reduction of SOD activity and interference with glutathione metabolism. In a model of PMA

application to mouse skin, resveratrol induced the restoration of  $H_2O_2$  and glutathione levels, and also myeloperoxidase, glutathione reductase and SOD activities (Jang.M et.al, 1999). The development of skin cancer is related to accumulative exposure to solar UVB as well as the nuclear transcription factor NF- $\kappa$ B, which plays a critical role in skin biology. NF- $\kappa$ B involved in the inflammatory and carcinogenic signalling cascades, and resveratrol was able to block the damage caused by UVB exposure via its antioxidant properties preventing UVB-mediated NF- $\kappa$ B activation. Finally, resveratrol could inhibit tumour progression, partly by an inhibition of DNA polymerase and deoxyribonucleotide Synthesis through its ability to scavenge the essential tyrosine radical of the ribonucleotide reductase and partly by inducing cell cycle arrest (Figure II).

## 5. EFFECTS OF RESVERATROL ON INTRACELLULAR REDOX STATE

Recent results have provided interesting insight into the effect of resveratrol on intracellular redox state. These findings seem to support both anti- and pro-oxidant activities of this compound, depending on the concentration of resveratrol and the cell type, leading to oxidative breakage of cellular DNA. Lately, it has been proposed that such pro-oxidant action could be an important action mechanism of it's anticancer and apoptotic inducing properties. Furthermore, it has been shown that there is an interesting correlation between the antioxidant and pro-oxidant activities and cytotoxicity of dietary polyphenols (Zheng, L.F et.al, 2006). Every antioxidant is, in fact, a redox (reduction–oxidation) agent and thus, might become a pro-oxidant to accelerate LP and induce DNA damage under special conditions. Studies have revealed pro-oxidant effects of antioxidant vitamins and several classes of plant-derived polyphenols such as flavonoids (Rahman A. et al., 1990), tannins (Singh S. et al., 2001) and curcumin (Ahsan. H et al., 1998).

Ahmad et al., 2003, observed that exposure of human leukaemia cells to low concentrations of resveratrol (4–8 $\mu$ M) inhibited caspase activation and DNA fragmentation induced by incubation with  $H_2O_2$ . At these concentrations, resveratrol elicited pro-oxidant properties as evidenced by an increase in intracellular  $O_2^-$  concentration. Likewise, in rat hepatocytes exposed to ferryl myoglobin-induced oxidative stress, physiological concentrations (100 pM–100 nM) of resveratrol exerted pro-oxidant activities. It also has been shown that resveratrol has a pro-oxidative effect on DNA damage during interaction with ADP- $Fe^{3+}$  in the presence of  $H_2O_2$  in tumour cell line cultures (Gusman J. et.al., 2001).

Similarly, the pro-oxidant effects of resveratrol were shown on rat liver microsomal systems. Resveratrol inhibited LP, however, resveratrol increased OH generation, indicating that OH played a minor role in LP (Ozgova et al., 2003). Besides, it is well known that haem (iron-protoporphyrin IX) is a pro-oxidant and its rapid degradation by haem-oxygenase is believed to be neuroprotective. Using primary neuronal cultures, resveratrol was able to induce significantly haem oxygenase. This study indicated that the increase of haem oxygenase activity by resveratrol is a unique pathway by which this compound can exert its neuroprotective actions (Zhuang H. et al., 2003). Further corroborating the pro-oxidant activity of resveratrol, some data that demonstrate it's inefficiency in protecting proteins (BSA) from oxidative damage induced by metal-catalysed reaction or alkyl peroxy radicals (Mayo et al., 2003). Fukuhara and Miyata first reported the pro-oxidant activity of resveratrol in a plasmid-based DNA cleavage assay in the presence of transition metal ions such as copper. DNA degradation by resveratrol in the presence of copper (10–100  $\mu$ M) or alone (200  $\mu$ M) (in the absence of added copper) has also been shown in a cellular system of peripheral lymphocytes isolated from human blood (Azmi et al., 2005; Azmi et al., 2006).

Copper is one of the most redox-active metal ions present in the nucleus, serum and tissues (Yoshida et al., 1993). Approximately 20% of copper is located in the nucleus and is closely associated with DNA bases, in particular, guanine (Agarwal K. et al., 1989). Furthermore, it has been shown that the concentration of copper is greatly increased in various malignancies (Azmi et al., 2005). Copper ions from chromatin can be mobilized by metal-chelating agents, giving rise to internucleosomal DNA fragmentation, a property that is the hallmark of cells undergoing apoptosis.

The cytotoxic mechanism of resveratrol probably involves mobilization of endogenous copper ions, possibly chromatin-bound copper. First, resveratrol undergoes oxidation in the presence of Cu(II). The oxidative product of resveratrol is a dimer, which probably formed by dimerization of resveratrol phenoxyl radical as a result of the reductive activation of molecular oxygen. Indeed, this initial electron transfer generates the reduction of Cu(II) to Cu(I). Interestingly, DNA strand scission occurred at neutral pH, indicating that resveratrol can induce DNA cleavage without the oxygenation of the benzene nuclei to the catechol moiety. However, the structural feature of the copper–peroxide complex as the reactive species responsible for the DNA cleavage is still unknown. Secondly,



the Cu(II)-peroxide compound is capable of binding DNA and forms a DNA-resveratrol-Cu(II) ternary complex. The high binding affinity of a 4-hydroxy group at the 4-position with both Cu(II) and DNA makes it possible and, therefore, cleaves DNA efficiently (Fukuhara K. et.al, 2006) (Figure III).

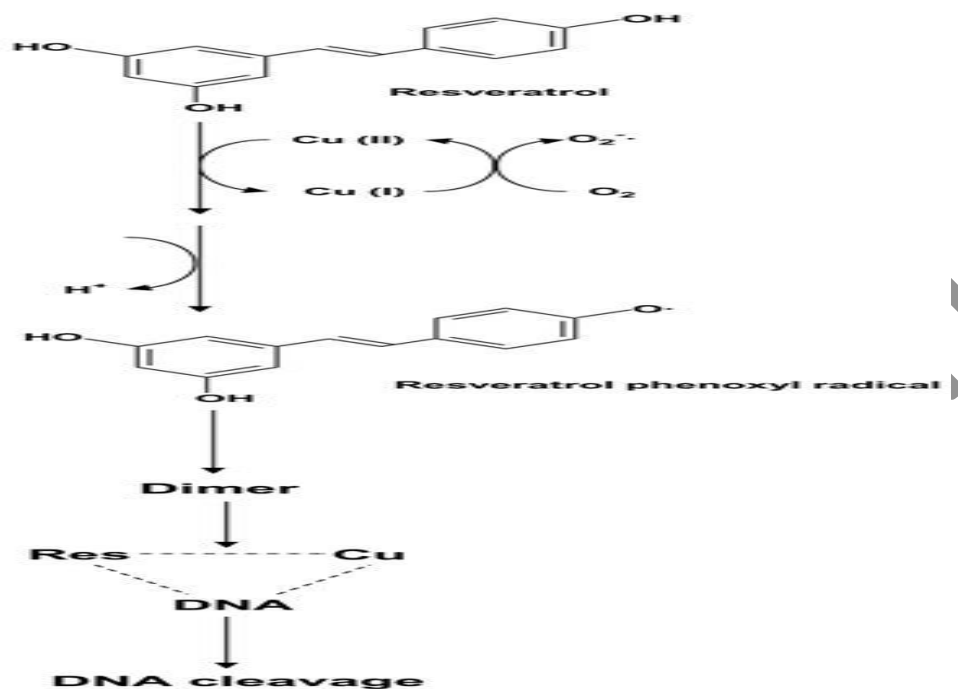


Fig. 5.1 Cytotoxic Mechanism of Resveratrol Probably Involves Mobilization of Endogenous Copper Ions

## CONCLUSION

The body of evidence presented here speaks volumes about the clinical potential of resveratrol as an antioxidant and pro-oxidant. Insufficient activation of apoptosis because of defects in apoptosis programmes or because of the dominance of survival signals may result in cancer cell resistance. Despite aggressive therapies, the resistance of many tumours to current treatment protocols still constitutes a significant problem in cancer therapy. Poly-mechanistic phytochemicals such as resveratrol may offer the advantage over targeted therapeutics and may open new perspectives in cancer therapy. By blocking survival and anti-apoptotic mechanisms or causing DNA degradation, as a consequence of its pro-oxidant action, resveratrol can sensitise cancer cells, which may result in synergistic antitumour activities when resveratrol combined with conventional chemotherapeutic agents or cytotoxic compounds (Cal C. et al., 2003). However, further insights into the signalling network and interaction points modulated by resveratrol may provide the basis for innovative discovery programmes to exploit resveratrol for the prevention and treatment of human diseases.

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