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Chemoprevention of Cancer and Cardiovascular Disease by Resveratrol

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ABSTRACT

Resveratrol (trans-3,4',5-trihydroxystibene) is a phytopolyphenol isolated from the seeds and skins of grapes. Recent studies indicate that resveratrol can block the process of multistep carcinogenesis, namely, tumor initiation, promotion and progression. Resveratrol can also reduce the risk of cardiovascular disease in man. The molecular mechanisms of resveratrol in chemoprevention of cancer and cardiovascular disease are interesting and under intensive investigation. Resveratrol was found to strongly inhibit nitric oxide (NO) generation in activated macrophages, as measured by the amount of nitrite released into the culture medium, and resveratrol strongly reduced the amount of cytosolic inducible nitric oxide synthase (iNOS) protein. The activation of nuclear factor κ B (NF κ B) induced by lipopolysaccharide (LPS) was inhibited by resveratrol. The phosphorylation and degradation of nuclear factor inhibitor κ B α (I κ B α) were inhibited by resveratrol simultaneously. Reactive oxygen species (ROS) are regarded as having carcinogenic potential and have been associated with tumor promotion. Resveratrol may act as a reactive oxygen species scavenger to suppress tumor development. In addition, resveratrol may block multistep carcinogenesis through mitotic signal transduction blockade. Reactive oxygen species are pivotal factors in the genesis of heart disease. Meanwhile, efficient endogenous antioxidants, including superoxide dismutase (SOD), glutathione peroxidase (GSHPx), and catalase, are present in tissues. A fine balance between reactive oxygen species and endogenous antioxidants is believed to exist. Any disturbance of this balance in favor of reactive oxygen species causes an increase in oxidative stress and initiates subcellular changes, leading to cardiomyopathy and heart failure. The experimental results indicate that exogenous antioxidant resveratrol is of value in chemopreventing the development of heart disease. It is urgent that more efforts be made to investigate newer therapies employing antioxidants for the chemoprevention of cardiovascular disease and cancer.

Key Words: chemoprevention, cancer, cardiovascular disease, resveratrol, ROS, antioxidants, inducible NO synthase, NF κ B

I. Introduction

Resveratrol (trans-3,4',5-trihydroxystibene) (Fig. 1) occurs naturally in grapes and a variety of medicinal plants. In plants, resveratrol functions as a phytoalexin that protects against fungal infection (Hain *et al.*, 1990). Because of its high concentration in grape skin, significant amounts of resveratrol are present in wine. *In vivo*, *ex vivo* and animal experiments have shown that resveratrol possesses many biological attributes that favor protection against atherosclerosis, including antioxidant activity, modulation of hepatic apolipoprotein and lipid synthesis, inhibition of platelet aggregation and the production of pro-atherogenic eicosanoids by human platelets and neutrophils (Soleas *et al.*, 1997). It also has been reported to have cancer

chemopreventive activity (Jang *et al.*, 1997). This review focuses on the effect of resveratrol on chemoprevention of cancer and cardiovascular disease.

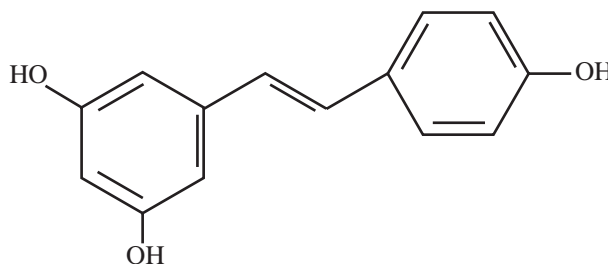


Fig. 1. Structure of resveratrol.

II. Mechanism of Cancer Induction

It has been established that most human cancers are induced by environmental factors, including chemicals, radiation and biological agents. The biochemical and molecular mechanisms of multistage carcinogenesis are very complicated. Most environmental carcinogens, such as aflatoxins, polycyclic aromatic hydrocarbons, and nitrosamines, are procarcinogens which have to be metabolically activated by mixed functional oxidase Cytochrome p450 to become electrophilic active carcinogens. The interaction of this electrophilic carcinogen with genomic DNA forms carcinogen-DNA adducts, which may lead to oncogene activation or tumor suppressor gene inactivation. It has been demonstrated that tumor initiation and promotion may result from oncogene activation, tumor suppressor gene inactivation or both.

The reactive oxygen species (ROS) have been considered as major pivotal determinants in the processes of tumor development. ROS, of course, arise whenever the cell is involved in oxygen utilization in its conversion of water, and this production may be enhanced by drugs, xenobiotics and diseases (Ames *et al.*, 1993). ROS are actively involved in the metabolic activation of procarcinogens and the processes of tumor initiation, promotion and progression.

Several lines of evidence indicate that oncogene mutation leading to protooncogene activation and tumor suppressor gene inactivation may play a crucial role in tumor initiation, promotion and progression. ROS are generally regarded as having carcinogenic potential and has been associated with tumor promotion. Some tumor cells produce ROS although the source of these products and their contribution to the transformed and malignant phenotype is not completely known. Certain kinds of ROS have been shown to act as essential intracellular second messengers for several cytokines and growth factors (Sundaresan *et al.*, 1995). Thus, antioxidants, such as superoxide dismutase, catalase, tea polyphenols, vitamins (Vit.) C, Vit. E, and others, may be protective against cancer and may inhibit cell proliferation, and the intracellular ROS scavenger may actually contribute to suppression of tumor development.

The implication of ROS as a mediator of ras-induced cell cycle progression independent of mitogen-activated protein kinase (MAPK) and c-Jun NH₂-terminal kinase (JNK) suggests another possible mechanism for the effect of antioxidants against ras-induced cellular transformation in tumor promotion (Irani *et al.*, 1997). This is the first evidence that puts superoxide firmly into the ras pathway, which is one of the cell's most important growth-stimulating pathways. The ras pathway can contribute to cancer development if it become overactive, which may happen as a result of mutation in ras, the gene that encodes ras, or

changes in other oncogenic proteins that also send their signals through the ras pathway.

III. Chemoprevention of Cancer by Resveratrol

A newer dimension in the management of neoplasia is the increasing awareness that chemoprevention, which refers to the administration of chemical agents to prevent the initiational and promotional events associated with carcinogenesis, may be the most direct way to reduce mortality and morbidity of cancer. The process of chemical carcinogenesis can be divided into three general stages, and chemopreventive agents have been categorized according to the stages that they inhibit (Wattenberg, 1993). Resveratrol is an antioxidant, and it may suppress tumor development through the removal of ROS. A recent report shows that resveratrol is a potent cancer chemopreventive agent in assays representing three major stages of carcinogenesis, and the ability to inhibit cellular events associated with tumor initiation, promotion and progression has been attributed to the anticycloxygenase activity cyclooxygenase-1, (Cox-1) of resveratrol. It has been found to induce phase II drug-metabolizing enzymes and to induce human promyelocytic leukemia cell differentiation. In addition, it has been found to inhibit the development of preneoplastic lesions in carcinogen-treated mouse mammary gland in culture and to inhibit tumorigenesis in a mouse skin cancer model (Jang *et al.*, 1997).

Resveratrol was found to act as a potential inhibitor of inducible NO synthase (iNOS) and inducible Cox-2 (Subbaramaiah *et al.*, 1998; Tsai *et al.*, 1999). Since physiological activity of iNOS and Cox-2 may benefit the organism, aberrant or excess expression of either iNOS or Cox-2 has been implicated in the pathogenesis of many disease processes, such as carcinogenesis and cardiomyopathy (Chhatwal *et al.*, 1994; Dubois *et al.*, 1996; Takahashi *et al.*, 1997). Because iNOS and Cox-2 are essential components of the inflammatory response, which can ultimate repair of injury and carcinogenesis (Moncada *et al.*, 1991; Anggard, 1994; Nathan and Xie, 1994; Seibert and Masferrer, 1994; Salvemini *et al.*, 1994; Tamir and Tannenbaum, 1996).

Strong antiproliferative properties of resveratrol have been found, and they are likely to be due to its ability to efficiently scavenge the essential tyrosyl radical of the small protein of ribonucleotide reductase and, consequently, to inhibit deoxyribonucleotide synthesis (Fontecave *et al.*, 1998). The ribonucleotide reductase provides proliferating cells with deoxyribonucleotides required for DNA synthesis during the early S-phase of the cell cycle (Reichard *et al.*, 1987). Another report shows that resveratrol may have therapeutic potential against liver injury through regulation of functions of hepatic stellate cells and kupffer cells

Chemoprevention of Diseases by Resveratrol

(Kawada *et al.*, 1998). In addition, Clément *et al.* (1998) have reported on a fascinating new facet of resveratrol. Using several experimental approaches, Clément *et al.* (1998) found that resveratrol acts as a cancer chemopreventive as well as a chemotherapeutic agent in humans. It has been found to induce apoptotic cell death in HL 60 leukemia cells as well as in T47D breast carcinoma cells at doses minimally toxic to normal peripheral blood lymphocytes (PBLs).

IV. Oxidative Stress and Heart Disease

ROS, such as single oxygen, superoxide radical, hydrogen peroxide, hydroxyl radical, nitric oxide and peroxyxynitrite, are highly unstable and extremely reactive. The wide distribution of these species makes them highly toxic for tissues, including the heart (Kaul *et al.*, 1993). Early *in vivo* studies examined the role of catecholamines in stress-induced heart disease and provided evidence that cardiac dysfunction may be mediated by the production of ROS initiated by autooxidation of catecholamines (Singal *et al.*, 1983). About the same time, the role of ROS in ischemia-reperfusion injury was demonstrated and was shown to be mediated by depressed Ca^{2+} transport in the sarcoplasmic reticulum (Hess *et al.*, 1983). These studies formed the basis for a multitude of studies on the role of ROS in the pathogenesis of cardiomyopathies and heart failure.

Under normal conditions, 3-5 % of the oxygen taken up by the cell undergoes univalent reduction leading to the formation of ROS. However, tissue concentrations of ROS are limited by a system of enzymatic and non-enzymatic antioxidants and ROS scavengers that have developed and been conserved during the evolution of aerobic life. Three of the most important cellular antioxidant enzymes are superoxide dismutase (SOD), glutathione peroxidase (GSHPx) and catalase.

In pathological or disease conditions, such as diabetes, heart failure and others, the production of ROS may override the scavenging effects of antioxidants, leading to a condition known as oxidative stress (Kaul *et al.*, 1993). Many experimental studies have demonstrated that increased oxidative stress and depressed antioxidant status have deleterious effects on both cardiac structure and function (Kaul *et al.*, 1993). Clinical studies on heart failure patients have also provided support for the role of ROS in the pathogenesis of heart failure. The usefulness of antioxidant therapy, especially Vit. E, in attenuating the progression of heart failure has been reported (Axford-Gatley and Wilson, 1991; Stampfer *et al.*, 1993).

Although there are many gaps in our understanding of the role of ROS in the pathogenesis of cardiopathies and heart failure, based on the available data, the following conclusion can be made. Any acute or chronic cardiac

stress conditions, resulting in a relative deficit in the myocardial antioxidant reserve, are associated with an increase in myocardial oxidative stress. The latter is capable of causing subcellular abnormalities that may induce cardiomyopathic changes, depressed contractile function and heart failure. Furthermore, the available evidence from animal and human studies illustrates that different antioxidants constituting an antioxidant reserve offer protection against oxidative stress-mediated myocardial changes. It is expected that further elucidation of the molecular basis of antioxidant changes will aid the development of newer therapies for modulating the pathogenesis of heart failure (Singal *et al.*, 1998).

V. Chemoprevention of Cardiovascular Disease by Resveratrol

Resveratrol has been proposed to explain, at least in part, the apparent ability of moderate consumption of red wine to reduce the risk of cardiovascular disease (Frankel *et al.*, 1993a, 1993b; Bertelli *et al.*, 1995; Pace-Asciak *et al.*, 1995). It has been suggested that it plays a role in the prevention of heart disease, as it inhibits platelet aggregation, alters eicosanoid synthesis and modulates lipid and lipoprotein metabolism (Soleas *et al.*, 1997). The role of platelets in initiating chemical signals that set in motion complex cellular events, resulting in atherosclerosis, following their adherence to the endothelial surface of arteries, as well as in triggering luminal occlusion, leading to acute coronary heart disease (CHD), is well established (Renaud *et al.*, 1992; Elwood *et al.*, 1991). The potential of platelets to adhere to vascular endothelium as well as to participate in blood coagulation and thrombus formation can be measured based on their ability to aggregate *in vitro* in response to a number of agonists. Using ADP and thrombin as agonists, Pace-Asciak *et al.* (1995) demonstrated a dose-dependent inhibition by resveratrol of the aggregation of platelets prepared from healthy human subjects.

Two major pathways for the synthesis of eicosanoids from arachidonic acid are present in human platelets. The cyclo-oxygenase pathway leads to the production of thromboxane A_2 , which plays an important role in propagating aggregation. Once this process has been initiated, the half-life of this component is extremely short, so that reproducible quantities are very difficult to obtain. Measuring the production from labeled arachidonate of thromboxane B_2 and hydroxyheptadecatrienoate (HHT), which are stable products formed from thromboxane A_2 , can, however, enable us to assess the overall activity of the pathway. The other pathway from arachidonate expressed in platelets involves the 12-lipoxygenase enzyme system, which synthesizes a family of eicosanoids defined as hepoxillins, which are mediators of calcium mobilization, vascular permeability and neutrophil activation. Its overall activity is

most frequently assessed by measuring the production of 12-hydroxyeicosatetraenoate (12-HETE), a stable compound which is thought to be pro-atherogenic through impairment of the endothelial function and prostacyclin production. Resveratrol was found to strongly inhibit cyclooxygenase pathway, approximately 60% at a concentration of 10 μ M, but did not stop the production of 12-HETE (Pace-Asciak *et al.*, 1995). In summary, resveratrol at micromolar concentration is able to inhibit thromboxane A₂ production. However, it is unable to inhibit the formation of heparin.

Oxidative modifications of low density lipoprotein (LDL) that alter physicochemical and biological properties of the LDL molecules are thought to play a central role in atherogenesis (Steinberg *et al.*, 1989; Parthasarathy and Rankin, 1992). The natural (native) form of LDL is subject to receptor-mediated endocytosis through a tightly regulated system, the LDL-receptor. During its transit in circulation, oxidative changes may occur, affecting the lipids and also the free lysine groups of apolipoprotein B. This "oxidized" LDL is taken up by endocytosis, mediated by a "scavenger" receptor system which is unregulated, resulting in over-accumulation of LDL in sub-endothelial cells, which derive from the monocyte lineage but because of their engagement with lipid, have come to be known as "foam cells" (Steinberg *et al.*, 1989). Oxidized LDL has other attributes conducive to atheromatous changes, including blocking of reverse cholesterol transport (uptake) by high density lipoprotein (HDL) and chemotactic properties promoting adhesion of platelets to the superficial endothelium (Witztum, 1994; Steinberg, 1992). Belguendouz *et al.* (1997) demonstrated that resveratrol was very efficient in protecting porcine LDL against polyunsaturated fatty acid (PUFA) peroxidation. Similar results were also obtained by Frankel *et al.* (1993a, 1993b); however, there were some differences in efficiency in inhibiting the formation of hexanal during copper-catalyzed oxidation of human LDL.

Using monolayer culture of Hep G2 cells, which retain most of the functions of normal liver parenchymal cells, in particular those related to lipoprotein synthesis and secretion (Gaziano, 1994; Hahn and Goldberg, 1992). Goldberg *et al.* (1995) found that the intracellular content and the rate of secretion of cholesteryl esters as well as the rate of secretion of triglycerides were reduced by resveratrol in a dose-dependent manner, but that the intracellular triglyceride content was unaffected. Thus, it tended to diminish the rate of secretion of very low density lipoprotein (VLDL), which are converted to atherogenic LDL in circulation, suggesting that resveratrol has the capacity to block certain aspects of hepatic lipoprotein metabolism, which lead to atherosclerosis.

Gehm *et al.* (1997) reported on a fascinating new facet of resveratrol. On the basis of the structural similarity

of resveratrol to the synthetic estrogen diethylstilbestrol, these authors hypothesized that it might be a phytoestrogen (Gehm *et al.*, 1997). Given the known cardioprotective benefits of estrogens, this idea is particularly appealing (Lobo, 1995). Resveratrol was found to act as effectively as estradiol in stimulating progesterone receptor gene expression in MCF-7 breast carcinoma cells, but no superagonistic effect was found. In addition, it inhibited binding of ¹²⁵I-labeled estradiol to estrogen receptor (ER) in competition binding studies, using nuclear extracts of MCF-7 cells (Frankel *et al.*, 1994; Bertelli *et al.*, 1995). On the other hand, in comparison with MCF-7 cells, the superagonistic effect of resveratrol was less pronounced in BG-1 ovarian carcinoma cells, suggesting a partial tissue specificity (Jang *et al.*, 1997). Although the concentration of resveratrol with estrogenic properties may have undesirable side effect, it can result in the stimulation of human breast cancer cells. This study raises the interesting possibility that this phytoestrogen may contribute to the cardioprotective effects associated with red wine consumption.

VI. The Effects of Resveratrol on Transcription Factors

Resveratrol may have therapeutic potential for some diseases, including ischemia heart disease, atherosclerosis, acute coronary heart disease, and cancer. These effects may be mediated by its strong antioxidant activity (Frankel *et al.*, 1993a, 1993b; Pace-Asciak *et al.*, 1995; Rotondo *et al.*, 1998). Although oxygen is a necessary requirement for aerobic organisms, its more reactive metabolites, ROS, have been implicated in a number of diseases (Sun, 1990; Fjarber *et al.*, 1990). These ROS are formed in the mitochondrial electron transport chain and in the cyclooxygenase pathway, and by cellular enzymes, such as cytochrome P450 oxidase, xanthine oxidase and NADPH oxidase (Fjarber *et al.*, 1990; Trush and Kensler, 1991; Cross *et al.*, 1987; Bandy and Davis, 1990). A variety of oxygenous chemical and physical agents can also cause production of ROS (Floyd, 1990; Freeman and Crapo, 1982; Moares *et al.*, 1990; Mustafa, 1990). Moreover, various pathological conditions are associated with ROS-mediated events, such as cancer, aging, vascular disease, and various immune complex-mediated diseases (Sun, 1990; Trush and Kensler, 1991; Floyd, 1990; Bast and Goris, 1989; Cutler, 1991; Ames, 1989).

Recently, our group reported that resveratrol could protect against endotoxin induced inflammation by preventing the activation of nuclear factor κ B (NF κ B) (Tsai *et al.*, 1999). Activation of NF κ B is necessary for lipopolysaccharide (LPS) induction of the iNOS promoter (Xie *et al.*, 1994). NF κ B is composed mainly of two proteins: p50 and p65. In its unstimulated form, NF κ B is present in the cytosol bound to the inhibitory protein, nuclear

Chemoprevention of Diseases by Resveratrol

factor inhibitor κ B (I κ B). After stimulation of cells by a variety of agents, I κ B becomes phosphorylated, and this triggers a proteolytic degradation of I κ B. Serine phosphorylation of I κ B is sufficient for efficient degradation. On the other hand, stoichiometric phosphorylation of I κ B on tyrosine 42 does not cause a subsequent proteolytic degradation of the I κ B but, apparently, is sufficient to release I κ B from NF κ B and, hence, activate NF κ B (Imbert *et al.*, 1996). The mechanisms by which resveratrol can interfere with the activation of NF κ B are not clear. One possibility is that resveratrol may interact with ankyrin domains present in I κ B because the phosphorylation of I κ B is inhibited by resveratrol. Such an interaction could conceivably hinder I κ B phosphorylation and subsequent dissociation of NF κ B. However, whether resveratrol physically interacts with I κ B remains to be determined. Cells treated with LPS can generate ROIs by inducing NADPH oxidase activity, and ROS can activate protein tyrosine kinase (Bastian and Hibbs, 1994; Lee *et al.*, 1996). Furthermore, resveratrol has been found to possess potent protein kinase inhibitory activity and antioxidant activity (Miller and Rice-Evans, 1995; Chen *et al.*, 1990; Jayatilake *et al.*, 1993). A role for protein tyrosine kinase and ROIs has been implicated in NF κ B activation (Bastian and Hibbs, 1994; Baldwin, 1996). Therefore, resveratrol might inhibit the activation of NF κ B by inhibiting the LPS-induced phosphorylation and degradation of I κ B α .

Phorbol-12-myristate-13-acetate (PMA) with promoting activity leads to modification of several biosynthetic products and enzyme activities. It causes an increase in phospholipid turnover and in prostaglandin accumulation (Suss *et al.*, 1971; Furesten-berger and Marks, 1980; Verma *et al.*, 1980). PMA could activate protein kinase C (PKC) *in vitro* as well as *in vivo*, and PKC has been considered as the key enzyme for signal transduction in the processes of cell proliferation and differentiation (Kishimoto *et al.*, 1980; Castagna *et al.*, 1982). PKC is a lipid-activated kinase, which is known to play an important role in a wide variety of fundamental cellular processes, especially in transmembrane regulation of signal transduction (Nishizuka, 1989). Furthermore, several observations strongly suggest that PKC plays an important role in the cell transformation process (Fry *et al.*, 1985; Wolfman and Macara, 1987).

Phorbol esters, such as 12-0-tetradecanoylphorbol-13-acetate (TPA), stimulates the production of ROS by activating the ubiquitous membrane-bound NADPH oxidase system (Repine *et al.*, 1974; Troll *et al.*, 1982; Segal and Abo, 1993). A number of other studies have also demonstrated that free radical generation systems, such as xanthine/xanthine oxidase, can mimic the effects of phorbol esters in enhancing cell transformation in many cultured cells (Zimmerman and Cerutti, 1984; Cerutti, 1987; Pence and Reiners, 1987; Reiners *et al.*, 1987). Subbaramaiah *et al.* (1998) found that resveratrol acts as an inhibitor of

COX-2 by blocking PMA-induced translocation of PKC activity from cytosol to membrane. Resveratrol also was found to block the induction of c-Jun, and AP-1 activity was found to be suppressed by resveratrol (Subbaramaiah *et al.*, 1998). These inhibitory effects could be explained, in part, by the antioxidant properties of resveratrol as other phenolic antioxidants inhibit both phorbol ester-mediated activation of PKC and AP-1 (Lee and Lin, 1997; Huang *et al.*, 1991).

Platelet derived growth factor (PDGF) is known to be a potent mitogen for many kinds of cells (Friedman, 1993; Pinzani, 1995; Gressner, 1995). Activation of intracellular signal transduction by PDGF has been analyzed extensively in many kinds of cells (Marra *et al.*, 1994; Wong *et al.*, 1994; Bishayee *et al.*, 1989; Heldin *et al.*, 1989; Payne *et al.*, 1991). Phosphorylation of tyrosine residues of PDGF receptors and activation of MAP kinase play important roles in PDGF-stimulated growth of cells. A recent study showed that resveratrol inhibited PDGF/BB-stimulated phosphorylation of tyrosine residues of 180 kd proteins, presumably the PDGF receptor, and activation of MAP kinase (Kawada *et al.*, 1998). Resveratrol also was found to inhibit the activation of phospholipase C (PLC) under PDGF-BB stimulation. Because activation of the PKC-PLC pathway plays a part in the activation of MAP kinase through Raf-1 phosphorylation (Meisenhelder *et al.*, 1989; Koch *et al.*, 1991; Cowley *et al.*, 1994). Moreover, resveratrol can reduce the level of cyclin D1, a cell cycle-related protein (Kawada *et al.*, 1998). Proliferation of eukaryotic cells is generally controlled at the stage from G1 to S transition phases (Nasmyth, 1996; Stillman, 1996; Sherr, 1996; Hunter and Pines, 1994). G1 cyclins include three forms of cyclin D and cyclin E that are associated with Cdk (cyclin-dependent kinase) 2, Cdk4, or Cdk6. The present study showed that resveratrol selectively decreased the expression of cyclin D1 without affecting the levels of Cdk2, Cdk4, cyclin A, or cyclin E. Because cyclin D1 regulates the activity of Cdk4 and Cdk6, resulting in the phosphorylation of the retinoblastoma gene product Rb p110 and the successive G1- to S-phase transition, its reduction might cause G1 arrest in the cells. In summary, the present report shows that resveratrol regulates the activity of receptor tyrosine kinase and the expression of cell cycle protein cyclin D1, thereby modulating proliferation of cells.

VII. Conclusion

It has been demonstrated that many phenolic compounds present in food and vegetables possess potent and desirable biological activities against cancer and cardiovascular disease. The most universal property is related to their functions as antioxidants, manifested by their ability to trap free radicals and inhibit their enzymatic generation, and to

block the oxidation of cellular and extracellular compounds, such as membranes and LDL. There are several mechanisms that may account for the biological properties of resveratrol, such as anti-cancer, anti-cardiovascular disease, and anti-inflammation. The possible signal transduction pathway inhibited by resveratrol that may be mediated through (1) inhibition of stimulator interaction with its receptor, (2) scavenging ROS, and (3) inhibition of protein kinase. Finally, based on the finding that signal transduction may be affected by resveratrol, further studies are needed to determine how effective resveratrol or its analogus may be in preventing or treating inflammation, cardiovascular disease, and cancer.

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Chemoprevention of Diseases by Resveratrol

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葡萄酚對癌症與心血管疾病之預防作用

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葡萄酚(resveratrol)是從葡萄種子及其果皮分離出來的一種植多酚(phytopolyphenol)，據最近的研究指出葡萄酚可抑制多步驟之致癌作用，同時也可減少人類心血管疾病之危險機率。這些作用之分子機制正受到各方學者的研究。在吞噬細胞中，一氧化氮合成酶(iNOS)可受到葡萄酚之抑制。一氧化氮合成酶之活性受到NF κ B之調控。NF κ B之活性化與I κ B之磷酸化作用及其分解有密切的關係。在我們實驗室已證實葡萄酚可以抑制I κ B之分解。活性氧(reactive oxygen species, ROS)對致癌作用與心血管疾病之發生有密切的關係，內生性的抗氧化劑如superoxide dismutase、glutathione peroxidase及catalase對這些疾病之預防有很重要的貢獻，另外一些外生性的抗氧化劑如vitamin E、vitamin C、葡萄酚及其他植多酚對癌症與心血管疾病之預防上也佔有重要的地位。