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Review

Resveratrol: Chemoprevention with red wine

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Abstract

According to epidemiological studies, western diet has disadvantages because of cancer prevalence more than Mediterranean or Asia people who consume more vegetables and fruits. Resveratrol (trans-3,4,5-trihydroxystilbene) which is highly found in grapes, berries has received attention for its potential chemopreventive and antitumor effects in experimental systems. Because of high resveratrol content, researchers noted that red wine has multidimensional benefits for cardiovascular health. Resveratrol also protects neuron cells from other well known chemotherapeutics. The molecular function of resveratrol in chemoprevention and carcinogenesis are reviewed by experimental cancer cell models. Resveratrol is going to be a promising molecule in future cancer prevention and therapy models.

Key words: Resveratrol, chemoprevention, carcinogenesis, apoptosis.

Introduction

Studies have shown that the incidence of cancer varies greatly between men living in western and far eastern countries. It has been suggested that this large difference in incidence may be attributed to the vastly different diets consumed by the men living within these countries (Go *et al.,* 2003; Jang *et al.,* 1997). Men living in western countries consume a diet with a higher fat content and lower fruit and vegetable intake than men living in far eastern countries.

A number of epidemiologic studies have suggested that daily nutrition uptake habits plays an important role in carcinogenesis and that 30 % of cancer morbidity and mortality can potentially be prevented with proper adjustment of diets (Miller and Rice-Evans, 1995). Researchers believe that the reason for this observation is the presence of phytochemicals that are found naturally within certain fruits, vegetables, and legumes (Langcake and Pryce, 1977; Peterson and Dwyer, 1988). As good examples, genistein, coumestrol, quercetin, zearalenone, and resveratrol exerted genotoxic effects in *in vitro* test systems (Go *et al.,* 2003; Jang *et al.,* 1997; Surh, 2003). Other phytoestrogens such as lignans, the isoflavones, daidzein and glycetein, anthocyanidins, and the flavonol fisetin exhibited only weak or no effects *in vitro* (Stopper *et al.,* 2005). Practically all of the phytoestrogens exhibit pro-apoptotic effects in some cell systems (Giri and Lu, 1995). Especially during menopause, this kind of nutrition types favored by women who are concerned about the side effects of hormone replacement therapy (Jang *et al.,* 1997;Stopper *et al.,* 2005). However, adverse health effects of phytoestrogens have often been ignored.

There is extended discussion of the genotoxic potential of estrogens to phytoestrogens, which occur in numerous plants, and today are considered to be potent candidates in the field of chemoprevention as a friend. Rather high concentrations of phytoestrogens are found in many diets, especially in Asia, where the diet contains high amounts of soy and leguminosae. Other phytoestrogens are found in fruits, mulberries, and vegetables (e.g. resveratrol, anthocyanins, flavanons). It has been proposed that dietary phytoestrogens could play a role in prevention of estrogen-related cancers like breast cancer, prostate cancer, and to a lesser extent endometrial and testicular cancer (Li *et al.,* 1999). However, possible adverse effects have hardly been evaluated. Certain estrogenic compounds are capable of inducing neoplastic transformation in primary cells and are clearly carcinogenic in animals. Examples are the synthetic estrogen diethylstilbestrol and the mammalian estrogen 17β-estradiol (Cornwell *et al.,*

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2004). Both estrogens are associated with cancer in humans. Thus, the question has been raised whether carcinogenic estrogens have genotoxic effects in addition to their hormonal activity. In support of this hypothesis, diethylstilbestrol and 17β-estradiol have been shown to cause DNA-alterations *in vitro* and *in vivo* (Rimando *et al.,* 2004). Dietary components also may have positive or negative effects on the development of prostate cancer like other types of cancer (Go *et al.,* 2003; Jang *et al.,* 1997; Miller and Rice-Evans, 1995). Studies have shown that increased consumption of dietary fat promotes the development of cancer. On the other hand, research has shown that regular consumption of fruits and vegetables has an inhibitory effect on the development of cancer. This inhibition has been attributed to several different groups of compounds called phytochemicals that are found in fruits and vegetables. Examples of phytochemicals include resveratrol, which is found in grapes and leguminous products, and β-sitosterol, which is also found in plant oils and leguminous products. The β-sitosterol supplementation for 3 days activates the MAPK pathway in MDA-MB-231 breast cells, and stimulates the synthesis of prostaglandins in vascular smooth muscle cell (Awad *et al.,* 2005). Prostaglandins are ubiquitous compounds that are involved in a variety of inflammatory and homeostatic processes throughout the body. They are formed by the combined action of cytosolic phospholipase A2 (cPLA2) and the two isoforms of the cyclooxygenase protein (COX-1 and COX-2). COX-1 mediates physiological functions such as cytoprotection of the stomach and is constitutively expressed within most tissues, while COX-2 is an inducible enzyme that is up-regulated in response to mitogenic or inflammatory stimuli. High levels of COX-2 protein have been found in breast, colon, and prostate cancer tissues. The proposed mechanism by which COX-2 promotes carcinogenesis includes promoting angiogenesis, enhancing cellular motility and increasing resistance to apoptosis (Lithitayawuid *et al.,* 2002).

In briefly, these phytochemicals inhibit cancer cell growth by inducing apoptosis and inhibiting cell cycle progression. There are many *in vitro* studies which aim to show how these compounds are working (Jang *et al.,* 1997). For example, nutritional agents present in food, e.g. soy isoflavones, lycopene, vitamin E, selenium, vitamin D, green tea polyphenols and many more, have been found to inhibit proliferation or to induce apoptosis in some prostate cancer cell lines (Signorelli and Ghidoni, 2005). Epigallocatechin-3-gallate, a polyphenolic compound in green tea, increased apoptosis by >50 % compared with the control when assessed in DU-145 human prostatic cancer cells. Epigallocatechin-3-gallate effects in LNCaP cells are caused by a down-regulation of the expression of the androgen receptor. The results were similar for gallic acid in the present model. There was also a significant inhibition of proliferation of LNCaP cells with tannic acid (5 and 10 μmol/L). Tannins also have broad cancer chemopreventive activity in several animal models, acting as both an anti-initiating and anti-promoting agent. Other antitumour nutrients are genistein and biochanin A, quercetin, cathechin and epicathechin (Peterson and Dwyer, 1998; Stopper *et al.,* 2005; Cornwell *et al.,* 2004).

The resveratrol which is the most potent one is still under investigation to learn the exact molecular mechanism on cancer chemoprevention. The review of literature aims to reveal the genotoxicity and apoptotic effects of the most studied phytoestrogen, resveratrol is possible as a friend or enemy.

General survey to resveratrol

The mostly studied compound trans-3,4',5-trihydroxystilbene or resveratrol, a phytoalexin present in more than 70 plant species including grapes, peanuts, berries and pines. Fresh grape skin contains about 50-100 μg of resveratrol per gram wet weight (Baliga *et al.,* 2005). Therefore grape products such as red wine, has been identified as a chemopreventive and anti-carcinogenic beverage (Figure 1).

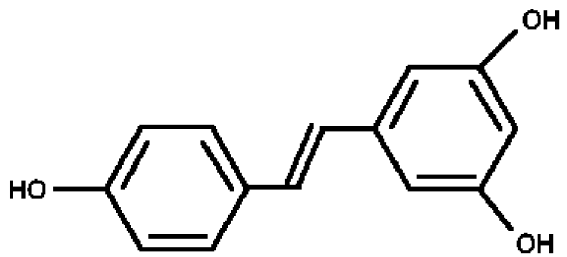

Figure 1. Resveratrol chemical formula

Resveratrol was first isolated from the roots of white hellebore (*Veratrum grandiflorum*) in 1940, the natural polyphenolic compound resveratrol was known as a plant antibiotic. It is generally produced in response to stress, such as fungal infection, UV radiation, and temperature changes (Bavaresco, 2003). Also Delmas *et al.* (2006) showed that resveratrol biosynthesis can be induced by the pathogen, *Botrytis cinera* infection (Delmas *et al.,*

2006). Generally resveratrol is present in high concentrations in fresh grape skin, and its concentration in specific types of red wine can reach up to 14 mg/L. Research over the past several decades has revealed that resveratrol exerts multifarious biological effects, including potent antioxidant, antiinflammatory, antiplatelet, and antiproliferative effects. It has some superestrogenic effects which was shown in *in vit*ro studies (Sgambato *et al.,* 2001; Signorelli and Ghidoni, 2005). Resveratrol is also called as anti-aging molecule, it extends lifespan in yeast, fish and mice (Howitz *et al.,* 2003; Valenzano and Cellerino, 2006; Baur *et al.,* 2006)

Resveratrol is a member of stilbenes as polyphenolic compound. The mostly detected form in plants as glycosylated piceid conjugates (3-O-B-D-glucosides). Other rarely seen forms contain 1-2 methyl groups (pterostilbene), a sulphate group (trans-resveratrol-3-sulphate) or a fatty acid have been also identified. Glycosyl groups are known to protect resveratrol from oxidative degredation and make stable and more soluble (Walle *et al*., 2004). Although these conjugated forms have longer plasma half life, their bioavailability and efficacy are still unknown (Baur and Sinclair, 2006). Trans-resveratrol has an advantage because of more efficient absorbition capacity in oral administration than other known polyphenols such as quercetin and catechin (Soleas *et al*., 2001). Numerous studies exist that have utilized a wide range of concentration of resveratrol suggesting that its biological activity effects may vary depending on cell and tissue types. For example, 32 nM and 100 μM have been used to study various effects of resveratrol *in vitro*, and 100 ng^{-1}, 500 mg per kg (body weight) for animal studies (Baur and Sinclair, 2006).

Molecular aspects of resveratrol in carcinogenesis

This polyphenol exhibits chemopreventive properties when tested in a mouse skin cancer model system and other cancer cell lines. It also affects the processes underlying all three stages of carcinogenesis; namely, tumor inititation, promotion and progression. Previous reports indicated that resveratrol can modulate multiple pathways involved in cell growth, apoptosis and inflammation (Seve *et al.,* 2005; Athar *et al.,* 2007). Extensive data in human cell cultures showed that resveratrol could suppress angiogenesis and metastasis. The anti-carcinogenic effects of resveratrol appear to be closely associated with its antioxidant activity, and it has been shown to inhibit COX, hydroxyperoxidase, protein kinase C, Bcl-2 phosphorylation, Akt, focal adhesion kinase, NF-κB, matrix metalloproteinase-9 and cell cycle regulators. *In vitro* and *in vivo* studies about resveratrol provide a rational in support of the use of resveratrol in human cancer chemoprevention especially in combinatorial approach with either chemotherapeutic drugs or cytotoxic factors for the highly efficient treatment of drug refractory tumor cells (Seve *et al.,* 2005). In other studies, resveratrol has been shown to inhibit cell growth by inducing apoptosis and cell cycle arrest in several tumor cells and arrested prostate cancer cells in the S-phase of the cell cycle and induced apoptosis (Sgambato *et al.,* 2001; Bowers *et al.,* 2000; Fulda and Debatin, 2005; Jones *et al.,* 2005). Resveratrol decreased the expression of cyclins D1 and D2, Cdk 2, 4 and 6, and proliferating cell nuclear antigen whereas p21WAF1/CIP1 was increased.

A number of cell types respond to resveratrol treatment by manifesting cell cycle arrest and apoptosis that partially is mediated through nitric oxide formation, which then interferes with endogenously produced reactive oxygen (Holian *et al.,* 2002). The signaling through protein kinase C alpha and delta activity also seems to be affected. Furthermore, some anti-apoptotic proteins such as surviving and markers of tumor promotion, ornithine decarboxylase were decreased after resveratrol treatment in cell culture models (Aziz *et al*., 2005).

Breast cancer

A kind of phytoestrogen, resveratrol can inhibit growth and induce apoptosis in melanoma cell lines (Hsieh *et al.*, 2005; Niles *et al.,* 2003). Resveratrol induced Fas/Fas ligand mediated apoptosis in breast cancer cell lines (Clement *et al.,* 1998). Also proapoptotic ceramide accumulation induces apoptosis after resveratrol treatment in breast cancer cells (Scarlatti *et al.,* 2003). Ceramide induces quinine reductase which is a phase II detoxification enzyme and induce caspase independent apoptosis through Bcl-2 down regulation (Bianco *et al.,* 2005; Pozo-Guisado *et al.,* 2005). It can bind alpha and beta estrogen receptors, and activates estrogen receptor-dependent transcription in human breast cancer cells (Le Corre *et al.,* 2005). In some cell types, such as estrogen receptor positive MCF-7 cells, resveratrol act as a superagonist, whereas in others, it produces activation equal to or less than that of estradiol. The obtained results from *in vitro* breast cancer cells exhibited that the chemopreventive effects of resveratrol likely to be very complex. Magee and Rowland (2004) showed that resveratrol can interfere with estrogen receptor

alpha associated PI3K pathway, following process that could be independent of the nuclear functions of estrogen receptor alpha (Pozo-Guisada *et al.,* 2004). Resveratrol also acts as an agonist for the cAMP/kinase-A system (El-Mowafy and Alkhalaf, 2003).

Colon cancer

In colon cancer, resveratrol activates various caspases and triggers apoptosis, which involves the accumulation of the pro-apoptotic proteins Bax and Bak and redistribution of the Fas receptor in membrane rafts (Delmas *et al.,* 2003). Also it can substantially downregulate telomerase activity (Fuggetta *et al.,* 2006). *In vivo* efficiancy of resveratrol was tested in Min mice model. The Min mice harbor a mutated Apc gene similar to that found in patients with familial adenomatous polyposis, and in many sporadic cancers (Corpet and Pierre, 2003). Administered orally at 0.01% in the drinking water for 7 days, resveratrol 70 % reduced formation of small intestine tumors and prevent colon tumor development. Similar results were obtained by Sale *et al.* (2005) which showed that the synthetic resveratrol analog 3,4,5,4'-tetramethoxystilbene (DMU-212) also inhibited the development of adenomas in the Apc (Min+) mouse (Athar *et al.,* 2007).

Prostate cancer

The effect of resveratrol has been demonstrated in various cultured prostate cancer cells, both hormone-sensitive and hormone-refractory, which mimic the initial or advanced stages of prostate carcinoma, respectively. These studies have shown that resveratrol substantially modulates the growth of these cells and alters the expression of more than one set of functionally related molecular targets. Resveratrol can repress different classes of androgen-responsive genes, including prostate-specific antigen (PSA), human glandular kallikrein-2, AR (androgen receptor)-specific coactivator ARA70, and p21WAF1/CIP1 in hormone-responsive cells (Mitchell *et al.,* 1999), activate p53-responsive genes such as PIG7, p300/CBP and Apaf-1 (Narayanan *et al.,* 2003), inhibit PI3K/AK activation, and increase Bax, Bak, Bid, and Bad (Aziz *et al.,* 2006). Generally, resveratrol has lots of roles on growth, induction of apoptosis, and modulation of prostate-specific gene expression using cultured prostate cancer cells that mimic the initial (hormone-sensitive) and advanced (hormone-refractory) stages of prostate carcinoma. When androgen-responsive LNCaP and androgen-nonresponsive DU-145, PC-3, and JCA-1 human prostate cancer cells were cultured with different concentrations of resveratrol (2.5×10^{-5}–10^{-7}M) their effects were observed for cell growth, cell cycle distribution, and apoptosis (Scifo *et al.,* 2004). Addition of 2.5×10^{-5}M resveratrol led to a substantial decrease in growth of LNCaP and in PC-3 and DU-145 cells, but only had a modest inhibitory effect on proliferation of JCA-1 cells. Flow cytometric analysis showed that resveratrol partially disrupt G_1/S transition in all three androgen-nonresponsive cell lines, but had no effect in the androgen-responsive LNCaP cells. In difference to the androgen-nonresponsive prostate cancer cells. However, resveratrol causes a significant percentage of LNCaP cells to undergo apoptosis and significantly lowers both intracellular and secreted PSA levels without affecting the expression of the AR. These results suggest that resveratrol negatively modulates prostate cancer cell growth, by affecting mitogenesis as well as inducing apoptosis, in a prostate cell-type-specific manner. Resveratrol also regulates PSA gene expression by an AR-independent mechanism (Fulda and Debatin, 2005; Jones *et al.,* 2005; Scifo *et al.,* 2004). According to our unpublished resveratrol results, estrogen or AR positive/negative cell lines give various responses against resveratrol treatments. Therefore the receptor status is main question to understand resveratrol efficiency rate in these cell lines. Resveratrol also down regulate PSA by a mechanism independent of changes in AR (Hsieh and Wu, 1999; Hsieh and Wu, 2000). However the interaction of resveratrol with AR is not clear (Kampa *et al.,* 2000). Moreover, resveratrol was shown to modulate Nitric oxide (NO) production (Kampa *et al.,* 2000) and prevent the increase in reactive oxygen species (ROS) (Sgambato *et al.,* 2001). Resveratrol treatment of various prostate cells was also accompanied with the activation of MAPK signaling, an increase in cellular p53 content, likely due to stabilization by serine-15 phosphorylation (Gao *et al.,* 2004; Lin *et al.,* 2002) ceramide associated growth inhibition (Sala *et al.,* 2003), the blockage of Stat3-mediated dysregulation of growth and survival pathways (Kotha *et al.,* 2006). Currently no preclinical studies have been reported on prostate carcinogenesis. We hypothesized that the inhibitory effect of these phytochemicals on growth is mediated, at least in part; by their effects on apoptosis mechanism may be via prostaglandin synthesis, and/or ROS formation.

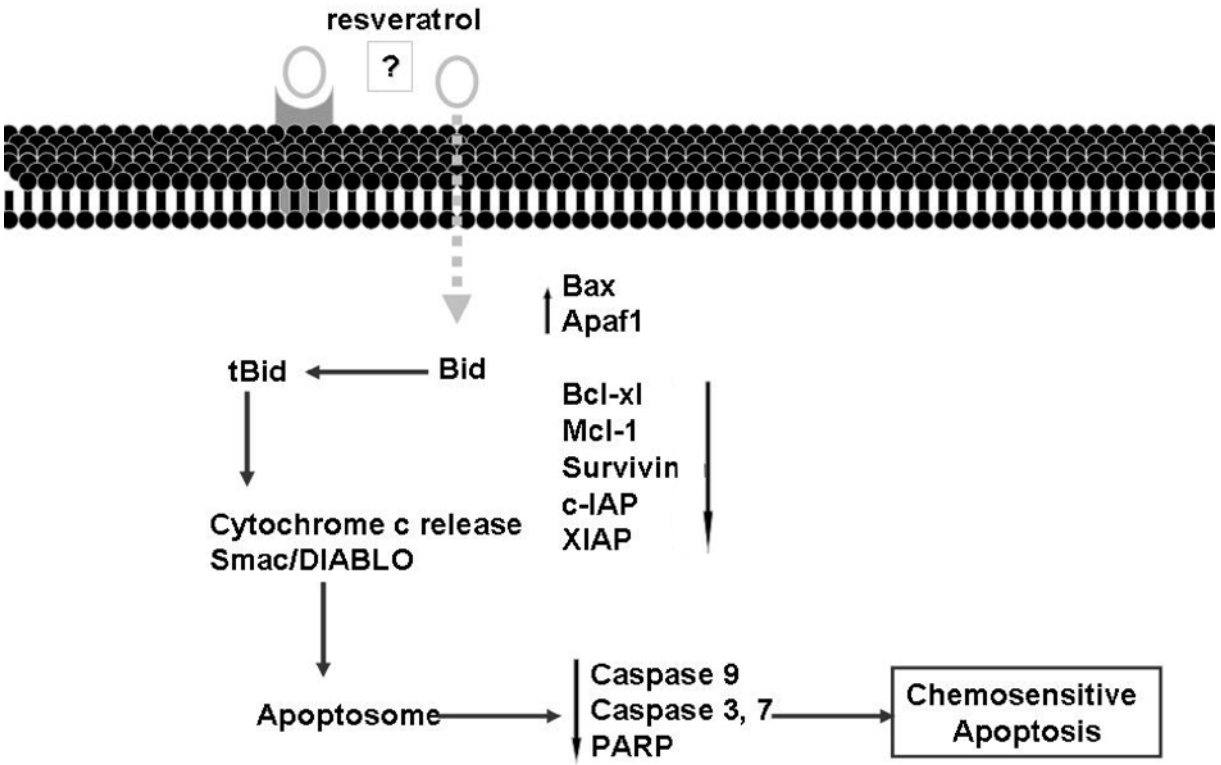

Figure 2. Resveratrol induce apoptosis. It is not clear how resveratrol molecule enter the cell. There are still investigation whether to answer a presence of unknown receptor or gate. The appropriate dose of resveratrol triggers apoptosis and cause chemosensitivity in cancer cells. Experimental results showed that resveratrol could induce pro-apoptotic Bax and downregulates anti-apoptotic Bcl-xl and Mcl-1. Bid is truncated to tBid form and cause Cytochrome c release which induce apoptosome formation. Previous studies indicated that resveratrol not only induce apoptotic pathways, downregulates survival signals such as survivin, inhibitor apoptosis protein family members, c-IAP and XIAP (Modified from Jazirehi and Bonavida, 2004).

Lung cancer

According to Athar *et al.* (2007), wine consumers have decreased risk of lung cancer because high resveratrol content than other beverage consumers. Resveratrol alters the expression of PAH (polycyclic aromatic hydrocarbons)-metabolizing genes, such as the cytochrome P450 1A1 (CYP1A1) and 1B1 (CYP1B1), microsomal epoxide hydrolase (mEH), and glutathione S-transferase P1 (GSTP1) genes, resulting in the altered formation of carcinogenic benzo[a]pyrene (BaP) metabolites in human bronchial epithelial cells (Mollerup *et al.,* 2001). It inhibits the expression of CYP1A1 and CYP1B1 and the generation of reactive diol-epoxides that can bind to DNA forming covalent adducts that cause structural alterations with mutations (Berge *et al.,* 2004). BaP is ubiquitous environmental pollutant and is also present in cigarette smoke. There are numerous carcinogens in cigarette smoke that are likely involved in the pathogenesis of this type of tumor. Interestingly, BaP metabolization requires the induction of cytochrome CYP1A1 through the activation of the AhR.

Induction of apoptosis

In previous subchapters, the molecular function of resveratrol in many type cancer cell lines was illustrated. Especially cytotoxic effect of this molecule depends on apoptotic regulation. Interestingly how resveratrol induce apoptosis is still not clear. It may interfere with apoptosis pathways both by directly trigger apoptosis-promoting signaling cascades and by blocking anti-apoptotic mechanisms. The other important point, many researchers examine a presence of receptor which resveratrol binds tightly. Perhaps in cell systems it may enter the cell directly (Jazirehi and Bonavida, 2004) (Figure 2). Resveratrol sensitize cancer cell lines by blocking survival and anti-apoptotic mechanisms. According to Fulda and Debatin (2006) resveratrol has been shown to promote

apoptosis by blocking expression of antiapoptotic proteins or by inhibiting signal transduction through the PI3K/AKT, MAPK or NF-κB pathway. However, despite the enormous progress achieved over the last years, the relative impact of the various biological activities of resveratrol in specific diseases or individual types of cancer remains to be explored in more detail. Therefore phytochemicals such as resveratrol may offer the advantage over targeted therapeutics that they simultaneously tackle cancer resistance from multiple angles and thus, may prove to be more.efficient to kill otherwise resistant cancer cells. Further insights into the molecular mechanisms of action of resveratrol will facilitate the development of resveratrol or its derivatives as experimental therapeutics, e.g. in combination chemotherapy, in the prevention and treatment of human diseases.

The importance of resveratrol in cardiovascular health

Recent findings indicate that resveratrol also imparts multidimensional benefits on the cardiovascular system. On the basis of its high resveratrol content, moderate consumption of red wine has been advanced as a reason for the relatively lower cardiovascular mortality and morbidity in French populations with considerable cardiovascular risk factors, a phenomenon known as the "French paradox" (Kopp, 1998). In animal models, oral administration of resveratrol for 2–3 weeks as well as acute pretreatment with resveratrol have been shown to reduce myocardial infarct size and improve LV function after global ischemia/reperfusion injury *ex vivo* (Ray *et al.,* 1999) and regional ischemic injury *in vivo* (Kaga *et al.,* 2005). Reduced myocardial oxidative stress (Ray *et al.,* 1999) reduced apoptosis (Sato *et al.,* 2002) and enhanced capillary formation (Kaga *et al.,* 2005) have been proposed as underlying mechanisms of resveratrol-induced cardioprotection. Administration of resveratrol followed by a washout period conferred ischemic preconditioning-mimetic minfarct-sparing benefits against ischemia/reperfusion injury in isolated-perfused hearts and reduced myocardial oxidative stress and apoptosis in a NO-dependent manner (Hattori *et al.,* 2002). Resveratrol pretreatment upregulated myocardial inducible NO synthase (iNOS) expression (Hattori *et al.,* 2002) and the involvement of iNOS in resveratrol-induced cardioprotection was confirmed in iNOS-/- mice (Imamura *et al.,* 2002). Subsequent studies have identified activation of adenosine A1 and A3 receptors (Das *et al.,* 2005), activation of the MAPK pathway (Das *et al.,* 2006) and myocardial induction of vascular endothelial growth factor (VEGF), Flk-1, endothelial NOS (eNOS), thioredoxin-1, and heme oxygenase-1 (HO-1) (Kaga *et al.,* 2005; Fukuda *et al.,* 2006) in response to resveratrol administration.

The protective role of resveratrol in neurodegeneration

To date, little research has been done to determine the mechanisms by which these phytochemicals exert their effects. Therefore resveratrol has been proposed as a potential chemopreventive agent and its antimutagenic and anticarcinogenic activity has been demonstrated in several models. The mechanisms responsible of these effects, however, remain to be elucidated. However in neuronal cells such as human neuroblastoma SH-SY5Y was shown to inhibit caspase 7 activation as well as degredation of poly-(ADP ribose)-polymerase which occur in cells exposed to paclitaxel, an anti cancer drug (Nicolini *et al.,* 2001). Therefore resveratrol behave like neuroprotective agents against chemotherapeutics exposure. That means if resveratrol use as a chemotherapeutic agent in combination with other drug, it may protect neuron cells from other chemotherapeutics toxic effect. In similar with this results, Rigolio *et al.* (2005) showed that induced S-phase arrest and prevented SH-SY5Y from entering mitosis, the phase of the cell cycle in which paclitaxel exerts its activity. Futhermore, phosphorylation of Bcl-2 and JNK-SAPK, which occurs after paclitaxel treatment was reversed by resveratrol (Nicolini *et al.,* 2003). However the protective effect of resveratrol on neuroblastoma cell line were not similar in stage 4 amplified MYCN neuroblastoma cell line. In this cell line, resveratrol decreased cell viability and induce cell cycle arrest and apoptosis, accompanied transiently up regulate p53 expression and nuclear translocation of p53, followed by induction of p21 (WAF-1/CIP-1) and Bax expression (Liontas and Yeger, 2004).

Conclusion

Cancer is a dynamic process that involves many complex factors, which may explain why a "magic bullet" cure for cancer has not been found. Death rates are still rising for many types of cancers, which possibly contributes to the increased interest in chemoprevention as an alternative approach to the control of cancer. The design and development of chemopreventive agents that act on specific and multiple molecular and cellular targets is gaining support as a rational approach to control cancer.

Nutritional or dietary factors have attracted a great deal of interest because of their perceived ability to act as highly effective chemopreventive agents. They are perceived as being generally safe and may have efficacy as chemopreventive agents by preventing or reversing premalignant lesions and/or reducing second primary tumor incidence. Many of these compounds appear to act on multiple tumor promoter-stimulated cellular pathways. Resveratrol stands alone in the field of polyphenolbased chemoprevention and/or chemotherapy: it is the most extensively studied molecule and apparently the least toxic. Clinical studies using purified resveratrol in the proper pharmaceutical form are necessary to certain the interest of resveratrol in the treatment of cancers. All of the data which were proposed chemopreventive properties of resveratrol underlines the need for further studies in order to finally define the possible beneficial outcomes of its use as dietary supplement for the general population.

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