COMMENTARY

A reappraisal of the potential chemopreventive and chemotherapeutic properties of resveratrol

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Resveratrol, a phytoalexin found in grapes and wines, has been reported to exhibit a wide range of pharmacological properties and is believed to play a role in the prevention of human cardiovascular disease (the so-called 'French paradox'). This molecule may also play a major role in both cancer prevention and therapy. In this review article we summarize the recent advances that have provided new insights into the molecular mechanisms underlying the promising properties of resveratrol. These include cyclo-oxygenase, nitric oxide synthase and cytochrome P450 inhibition, as well as cell cycle effects, apoptosis modulation and hormonal activity.

Introduction

Resveratrol (3,4',5-trihydroxystilbene) is a polyphenol synthesized by a wide variety of plant species, including aliments such as grapes, peanuts and mulberries, in response to injury, UV irradiation and fungal attack (1). Its stilbene structure is related to the synthetic oestrogen diethylstilbestrol. Resveratrol was identified in 1963 as the active constituent of the dried roots of *Polygonum cuspidatum*, also called Ko-jo-kon in Japanese, used since ancient times in traditional Chinese and Japanese medicine against suppurative dermatitis, gonorrhea, favus, athlete's foot and hyperlipemia (2).

Resveratrol was first detected in grapevines (*Vinis vitifera*) in 1976 (1), and then in wine in 1992 (3). It is synthesized in the leaf epidermis and the skin of grape berries, but not in the flesh (4). The time in contact with grape skins is the determining factor in resveratrol extraction during the fermentation process, and is shorter in white as compared with red wines. Resveratrol is therefore much more concentrated in red than in white wine. Fresh grape skins contain 50–100 mg resveratrol/g (5).

As epidemiological studies have shown an inverse correlation between red wine consumption and the incidence of cardiovascular disease—a phenomena known as the 'French Paradox'—it has been suggested that resveratrol might be the main active principle of red wine. Since then, *in vitro*, *in vivo*

and *ex vivo* experiments have demonstrated the numerous biological activities of this metabolite (Table I).

This review article will focus on the anticancer activity of resveratrol and its molecular mechanisms, since it is one of the most promising chemopreventive anticancer agents. Resveratrol also possesses chemotherapeutic activities. Indeed, numerous experiments have demonstrated its ability to block each step in the carcinogenesis process, namely tumour initiation, promotion and progression (15).

Effect of resveratrol on cyclooxygenase

Within the context of the search for new chemopreventive anticancer molecules, numerous plant extracts have been tested for their potential to inhibit cyclooxygenase (COX). This enzyme, also called prostaglandin H synthase, possesses a constitutive form (COX-1), and an inducible form also expressed constitutively in certain regions of the brain, the kidneys and in cancerous tissue (COX-2). It can produce pro-inflammatory substances by metabolizing arachidonic acid to prostaglandins (PGs). Prostaglandins stimulate tumour cell growth by increasing cell proliferation, promoting tumor angiogenesis and suppressing immune surveillance (26–28). Moreover, COX hydroperoxidase activity is responsible for promutagen bioactivation. For example, extrahepatic neoplasia can be induced by mutagens resulting from the oxidation of aromatic amines by COX-peroxidase activity.

Resveratrol non-competitively inhibits the cyclooxygenase activity of COX-1 in a concentration-dependent manner (29). In contrast with most non-steroidal anti-inflammatory drugs like aspirin and piroxicam, it also inhibits COX-1 hydroperoxidase activity and, to a lesser extent, COX-2 hydroperoxidase activity (15). On the other hand, resveratrol has no influence on the cyclooxygenase activity of COX-2, or at most only slightly enhances it (15,16).

Resveratrol blocks eicosanoid formation and malignant

Table I. Therapeutic activities of resveratrol

Antibacterial and antifungicidal activities (4)
Antioxidant activity (6)
Free radical scavenging (7,8)
Inhibition of lipid peroxidation (9)
Inhibition of eicosanoid synthesis (10,11)
Inhibition of platelet aggregation (10,12,13)
Chelation of copper (7,9,14)
Anti-inflammatory activity (15–17)
Vasorelaxing activity (18)
Modulation of lipid and lipoprotein metabolism (19)
Oestrogenic/anti-oestrogenic activity (20,21)
Inhibition of antigen-induced contraction of sensitized isolated guinea-pig trachea (22)
Inhibition of rat brain monoamine oxidase (23)
Inhibition of gastric rat H+,K+-ATPase (24)
Inhibition of protein-tyrosine kinase and protein kinase C (25)
Antitumoural activity (15)

transformation mediated by chemical carcinogens in cultured mouse embryo fibroblasts C3H10T1/2 (30).

The anti-inflammatory activity of resveratrol has been investigated *in vivo* in rats. Resveratrol strongly suppresses carrageenan-induced paw oedema in both acute and chronic phases (15). This effect is attributed to the impairment of PG synthesis via the direct, selective inhibition of COX-1. The oedema-suppressing activity of resveratrol is greater than that of indomethacin or phenylbutazone.

In contrast with the *in vivo* results on the rat paw oedema model, *in vitro* co-treatment with resveratrol (2.5–20 μM) inhibits a phorbol 12-myristate 13-acetate (PMA)-mediated increase in the production of PGE_2 by a direct dose-dependent inhibition of COX-2 activity and by the suppression of the increase in *COX-2* transcription without altering the amount of COX-1 (31). Similarly, the pre-incubation of resveratrol decreases arachidonic acid release and COX-2 stimulation in resident mouse peritoneal macrophages exposed to lipopoly-saccharide, PMA, O_2^- or H_2O_2 (32). This effect is associated with a marked reduction of PG synthesis, a phenomenon which may be explained not only by the inhibition of COX-1 and COX-2 activity, but also by the impairment of *COX-2* induction.

To elucidate the mechanism involved in the modulation of *COX-2* expression, transient transfections have been performed using human *COX-2* promoter luciferase or *COX-2* promoter deletion constructs (31). Resveratrol suppresses the PMA-mediated activation of *COX-2* transcription by inhibiting the protein kinase C (PKC) signal transduction pathway at multiple levels, namely the inhibition of PMA-induced translocation of PKC from cytosol to membrane and the suppression of the activator protein-1 (AP-1)-dependent transactivation of *COX-2* by the inhibition of the PMA-induced overexpression of c-*jun*, and perhaps by the induction of the expression of Fra, a subunit of the AP-1 complex less active than the c-jun subunit. However, a recent study suggests that resveratrol may have only a negligible effect against the PKC isoenzyme subfamily and may well inhibit the novel phorbol ester-responsive protein kinase D (33).

Resveratrol inhibits the COX peroxidase-mediated oxidation of phenylbutazone and benzidine to free radicals in a concentration-dependent manner on microsomial COX in the presence of H_2O_2 and buffer (34). Moreover, when this activating system is coupled to the *Salmonella typhimurium* TA98 mutagenesis assay, resveratrol inhibits revertant production by the aromatic amine 2-aminofluoren in a dose-dependent manner. Resveratrol is thus able to interrupt the initiation and/or promotion of carcinogenesis by blocking the COX-hydroperoxidase-mediated activation of pro-carcinogens to carbon- or nitrogen-centred electrophiles that may bind to DNA and induce gene mutation.

The inhibition of COX-2 hydroperoxidase activity and *COX-2* expression by resveratrol thus seems particularly relevant in the latter's antitumour initiation and promotion activities. Its antimutagenic action is complemented by its ability to induce monofunctionally quinone reductase, a phase II enzyme capable of metabolically detoxifying carcinogens (35).

Moreover, the antipromotional and anticarcinogenic properties of resveratrol can be partly attributed to its ability to enhance gap-functional intercellular communication in cells exposed to tumour promoters such as TPA (36). Indeed, the blocking of gap-junctional intercellular communication (GJIC), an important mechanism in tumour promotion, is affected by most tumour promoters, including TPA (37).

Effect of resveratrol on NO synthase

The contributory role of NO on tumour growth and metastasis was recently evaluated in a murine mammary tumor model (38). Tumour-derived endothelial NOS (eNOS) promotes tumour growth and metastasis by multiple mechanisms, such as the stimulation of tumour cell migration, invasiveness and angiogenesis. Increased NOS induction and activity have been observed in various human cancers. For example, enhanced expression of inducible *NOS* (*iNOS*) and *eNOS* have been demonstrated in human colorectal cancers and correlated with tumour growth and vascular invasion (39). Similarly, increased NOS induction and activity in human gynaecological cancers have been associated with increased malignancy (40).

Bacterial endotoxic lipopolysaccharide (LPS) is one of the most important stimuli for iNOS induction. The effect of resveratrol on LPS-activated macrophages has therefore been investigated by a number of scientists. Resveratrol dose-dependently reduces *iNOS* expression in this model, without affecting *COX-2* expression (34). It strongly inhibits NO generation in LPS-activated macrophages by reducing the amount of cytosolic iNOS protein and steady-state mRNA (41), notably by inhibiting the LPS-induced activation of NFκB. The latter is a member of the Rel transcription factor family enhancing *iNOS* transcription in LPS-activated macro-phages. Resveratrol also reduces the nuclear content of NFκB subunits and suppresses phosphorylation (inactivation) and degradation of IκBα, an inhibitory molecule sequestrating the Rel transcription factors in the cytoplasm as inactive complexes. Resveratrol may therefore protect cells against endotoxin-induced inflammation by preventing NFκB activation. It is noteworthy that the pleiotropic transcription factor NFκB plays a crucial role in the control of cell proliferation and apoptosis, and hence, oncogenesis (42). The LPS-induced activation of NFκB inhibition by resveratrol is also effective with other inflammatory agents, such as tumour necrosis factor (TNF), PMA, H_2O_2, okoid acid and ceramide (43). The suppression of NFκB coincides with suppression of AP-1 and the associated kinases. However, other results have failed to show any inhibition of the LPS-induced activation of NFκB. Rather, they demonstrate a post-transcriptional decrease in NO release, an increase in basal levels of TNF-α mRNA and protein and an enhancement of LPS-induced TNF-α mRNA and cytokine release (44). It has been suggested that, by acting as a COX-1 inhibitor, resveratrol may interfere with the negative feedback loop of prostaglandins, which down-regulates TNF-α production at the mRNA level. This agrees with the inhibition which is exerted by resveratrol on NO, observed in LPS-stimulated Kupffer cells, and which has been also attributed to a post-transcriptional process.

However, it contrasts with the strong simultaneously-observed inhibition of TNF-α release (45).

Resveratrol also inhibits NO production in mouse peritoneal exudate macrophages activated by LPS (46). Similar to the effects observed above, resveratrol at a non-cytotoxic concentration inhibits LPS-stimulated iNOS induction. However, in addition to being contradictory, these results suffer from the lack of studies carried out on tumours rather than on inflammatory models.

Effect of resveratrol on cytochrome P450 and AhR function

Resveratrol, added before the adjunction of 7,12-dimethyl-benzanthracene (DMBA), dose-dependently inhibits revertant

production in a *Salmonella typhimurium* strain TM677 in the presence of an S9 liver homogenate from Aroclor-1254 pretreated rats and of an NADPH-generating system (47). Similarly, resveratrol inhibits the development of DMBA-induced preneoplastic lesions in a dose dependent manner in a mouse mammary gland culture model of carcinogenesis (48,49).

The effect of resveratrol on aryl hydrocarbon receptor (AhR) function and *CYP1A1* transcription has been reported (50–53). Resveratrol antagonizes the transactivation of genes regulated by AhR ligands. This action has been verified in different cell types with various polycyclic aromatic hydrocarbons, such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, DMBA and benzo[*a*]-pyrene. The ability of resveratrol to bind to AhR and act as a competitive antagonist of this receptor is controversial. Moreover, if some authors have demonstrated that resveratrol suppresses *CYP1A1* transcription by preventing the conversion of the ligand-bound cytosolic AhR into its nuclear DNA-binding form, others have shown that the inhibitory activity of resveratrol rather takes place during the interaction between AhR and the transcriptional complex. The discrepancy between the available experimental results are likely to be due to technical differences in methodology. For instance, fully efficient competition between resveratrol and the AhR ligands is only achieved when resveratrol is pre-incubated with the cells before the addition of ligands.

Resveratrol is also able to directly inhibit CYP1A1 in microsomal human liver preparations and in microsomes isolated from benzo[*a*]pyrene-treated human hepatoma cells (51,54). However, treatment with dietary resveratrol after treatment with the tobacco-smoke carcinogens benzopyrene and 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone has failed to reveal any prevention of lung tumour multiplicity (55). This lack of effect may be attributed to the delayed treatment with the preventive agent.

Resveratrol antioxidant properties and effect on TPA-induced carcinogenesis

Resveratrol inhibits free-radical formation in human promyelo-cytic leukemia cells treated with TPA in a dose dependent manner (49,56). Similarly, reactive oxygen species production after phorbol ester stimulation is decreased in both oestrogen-dependent and -independent human breast cancer cell lines (57).

Resveratrol significantly reduces the number of skin tumours per mouse on a two-stage mouse skin cancer model in which DMBA is used as an initiator and TPA as a promotor (15). The epidermal hyperplastic response to TPA is inhibited through interference with pathways of reactive oxidants and, possibly, through the modulation of the expression of the proto-oncogene *c-fos* and *TGF-β1* (30). Resveratrol also inhibits the TPA-induced cell transformation of the JB6 P+ mouse epidermal cell line C1 41 in a dose-dependent manner (58).

The molecule protects *in vitro* low-density porcine and human lipoproteins against peroxidative degradation induced by copper or the free radicals 2,2′-azobis (2-amidinopropane) dihydrochloride (AAPH) or 1,1-diphenyl-2-picryl-hydrazyl (DPPH) by respectively chelating and scavenging mechanisms (7–9,14,49,59–61). It also inhibits the responses observed in a xanthine/xanthine oxidase assay system (49).

In tumour cell line cultures, resveratrol attenuates the cytotoxic effect of reactive oxygen species (57). However, resveratrol simultaneously has a great potential for mediating

Cu^{2+}-dependent DNA cleavage under aerobic conditions (62–64). If resveratrol acts as an antioxidant of membrane lipids and as an efficient scavenger of lipid peroxyl and carbon-centred radicals, it also has a pro-oxidative effect on DNA damage during interaction with ADP-Fe^{3+} in the presence of H_2O_2.

In the rats treated with the kidney-specific carcinogen $KBrO_3$, pre-treatment with resveratrol totally prevents oxidative damage to kidney DNA and eliminates the increase in relative weight induced by the carcinogen, so demonstrating antioxidant properties *in vivo* (65).

Effect of resveratrol on the cell cycle, cell proliferation and apoptosis

Resveratrol has strong antiproliferative properties in relation to various cell types. This may be explained in particular by a dose-dependent inhibition of ribonucleotide reductase activity (66). This property is likely to be due to resveratrol's capacity to scavenge the essential tyrosyl radical of the small protein ribonucleotide reductase. In both murine mastocytoma P-815 and human myelogenous leukaemia K-562 cells, the molecule exerts a strong inhibitory effect on DNA synthesis. Resveratrol has also been found to inhibit DNA polymerase (67), as well as ornithine decarboxylase, a key enzyme of polyamine biosynthesis that is enhanced in cancer growth (68).

In various human tumour cell lines, resveratrol inhibits cell growth and DNA synthesis in a dose dependent manner (69,70). It suppresses serum-dependent proliferation of cultured hepatic stellate rat cells in a non-toxic manner and inhibits their activation by perturbing the signal transduction pathways. Furthermore, resveratrol arrests the stellate cells in G_1-phase by selectively reducing the level of cell cycle protein cyclin D_1 (45).

Resveratrol shows high selectivity towards malignant cell lines versus normal fibroblasts, and its cytotoxic effect is independent of metabolization (71). Resveratrol also impairs 3T6 fibroblast proliferation and DNA synthesis (72). This has been correlated with a reduction in reactive oxygen species production, phospholipase A2 translocation, and subsequent arachidonic acid and PGE_2 synthesis stimulated by fetal calf serum or platelet-derived growth factor.

The induction of apoptosis triggered by resveratrol has been observed in numerous cell types (73). Caspase inhibitors block this resveratrol-induced cytotoxicity. Resveratrol-induced cell death coincides with the enhancement of *CD95L* (*Fas L*) expression and preferentially targets *CD95* (*Fas, APO-1*) high-expressing cells. On the contrary, a minimal level of cytotoxicity is observed in normal human peripheral blood lymphocytes with no change in *CD95* or *CD95L* expression. Resveratrol-induced cell death is consequently tumour-specific and involves the *CD95–CD95L* system as the apoptotic trigger. It has been suggested that this system could activate a series of intracellular events culminating in the death cascade composed of intracellular caspases. Resveratrol induces apoptosis in fibroblasts in which the expression of oncogenic *H-Ras* has been induced, an effect partly attributed to the inhibition of NFκB following the blockade of IκB kinase activity (74).

Resveratrol induces apoptotic cell death in HL-60 cells, preferentially in cells arrested in the G_0/G_1 phase (70). This has been linked to a gradual decrease in the anti-apoptotic oncoprotein Bcl-2 expression. However, a resveratrol-induced

arrest in HL60 cells at the S/G_2 phase transition and a subsequent increase in the number of cells in the G_1/S phases have also been reported (75). This effect has been attributed to an increase in cyclins A and E and inactive cdc2, without any modification of $p21^{WAF/CYP1}$ expression. Terminal differentiation has also been observed (76).

The stimulation of apoptosis has also been associated with an increased expression of the *p53* tumour suppressor gene (58,77,78). *In vivo* and *ex vivo* observations have confirmed the ability of resveratrol to modulate cell growth and apoptosis (79). In the case of Yoshida ascitic hepatoma cells, a lack of parallelism between *in vitro* and *in vivo* results has been observed and could be attributed to a low proliferative rate *in vitro*, an indirect pathway involving molecules produced by the host *in vivo* or an increase in CD95L levels when resveratrol is injected into tumour-bearing rats.

The prolonged daily administration of resveratrol to rats treated with azomethane significantly decreases the number and multiplicity of aberrant crypt foci (ACF) in colorectal mucosa by a mechanism involving changes in $p21^{WAF/CYP1}$ and *Bax* expression (80). In treated rats, the expression of Bax and $p21^{WAF/CYP1}$ are respectively enhanced in ACF and lost in normal mucosa. This suggests an induction of apoptosis in ACF associated with the protection of normal surrounding mucosa.

Resveratrol exhibits anti-leukaemic activity against some mouse and human cell lines by irreversibly inhibiting cell proliferation and inducing apoptosis (81). On the other hand, long-term exposure to much higher concentrations of resveratrol inhibits the clonal growth of normal haematopoietic progenitor cells only in a partially reversible manner and without inducing nucleosomal DNA fragmentation. In lethally irradiated mice injected with bone marrow cells, resveratrol *ex vivo* helps in purging leukaemia cells from bone marrow autografs without any significant loss in the haematopoietic activity of progenitor cells.

Discrepancies have been observed in the selective effect of resveratrol on highly invasive tumour cell lines with high metastatic capacities versus cell lines with lower metastatic capacities (82). It seems that the intrinsic metastatic potential of cancer cells might affect their response to resveratrol.

The hypothesis that the anticancer properties of resveratrol are partly due to a pro-apoptotic activity has been challenged by the observation that resveratrol prevents the apoptosis triggered in human erythroleukaemia K562 cells by the use of hydrogen peroxide, cisplatin, TGF-β1 and 5-hydroxieicosate-traenoic acid (83). All these latter induce apoptosis through the activation of 5-lipoxygenase and the modification of membrane properties that permit the specific recognition and elimination of apoptotic cells by macrophages (84). The anti-apoptotic activity of resveratrol has been correlated with its ability to competitively inhibit the 5α-lipooxygenase and COXs, so reversing the oxidative stress-induced increase in leukotriene B4 and PGE_2 concentrations. However, these observations have only been reported for this erythroleukaemia cell line.

Hormonal activity of resveratrol

On oestrogen-dependent cells

The *in vitro* influence of resveratrol on oestrogen-responsive human breast cancer cell lines and a human ovarian carcinoma has been studied (20). In the absence of oestrogen resveratrol, like estradiol, increases the expression of transfected oestrogen-responsive reporter genes in the oestrogen-responsive human breast cancer cell lines tested. The expression of the native oestrogen-regulated gene coding for pS2 and the progesterone receptor (PR) is also increased. This resveratrol-induced transcriptional activation is oestrogen receptor (ER)-dependent, requires an oestrogen-responsive element in the reporter genes and is inhibited by specific oestrogen antagonists. The intensity of the oestrogenic effect varies, depending on cell type.

If resveratrol acts as an oestrogen agonist by itself, it also acts as an oestrogen antagonist in the presence of oestrogen, and inhibits human breast cancer cell growth (20,85,86). Indeed, it antagonizes the growth-promotion and PR expression induced by 17-β-estradiol in MCF-7 cells at both the cellular (cell growth) and molecular (gene activation) level. The mechanism of this inhibition is not terminal differentiation. Moreover, resveratrol modulates the expression of several autocrine growth modulators and/or their receptors (transforming growth factor-α and β2, and the insulin-like growth factor I receptor) in the breast cancer cells studied. The mechanism could mainly be a direct competition with 17-β-estradiol for its receptor, but could also involve other activities like the prevention of ER binding to the oestrogen responsive element or the inhibition of ER-mediated transactivation. These effects are isomer dependent, with the *trans*-resveratrol being more active than the *cis* isomer.

The anti-oestrogenic mechanism is not the sole mechanism for the growth inhibiting effect of resveratrol on breast cancer cells. Indeed, resveratrol also inhibits the growth of human ER-negative breast cancer cell lines (57,85,87).

Despite the fact that resveratrol exerts a weak and partial agonism on isolated rat uterine ER, the oestrogenic *in vivo* effect on rats is still unclear. In some experiments, no oestrogenic effect was observed (88–90). On the contrary, the co-administration of resveratrol with 17-β-estradiol antagonized cholesterol lowering. In a recent study, however, resveratrol was able to prevent decreases in femoral bone strength in ovariectomized rats and to lower blood pressure by increasing dilatory responses to acetylcholine in ovariectomized, stroke-prone spontaneously hypertensive rats (91).

On androgen-dependent cells

Resveratrol effects on both androgen-responsive and non-responsive human prostate carcinoma cell lines have been compared (92). A decrease in cell growth observed in all the cell lines tested suggests a possible anti-oestrogenic action. In the androgen-responsive cell lines, resveratrol induces apoptosis, drastically lowers intracellular and secreted prostate-specific antigen (PSA) and diminishes the expression of $p21^{WAF/CYP1}$ and *pRB* (92–94). The androgen-receptor dependence in the reduction of PSA expression is not well established. Anyway, resveratrol negatively modulates prostate cancer cell growth by affecting the cell cycle and inducing apoptosis. In the case of androgen non-responsive cell lines the results are more controversial since the growth inhibition of cell lines varies drastically from one cell line, or even one experiment, to another (95).

Pharmacokinetic parameters of resveratrol

The average concentration of resveratrol in commonly available red wines is approximately 2.0–40.0 μM (96). Its plasma pharmacokinetics following oral administration of red wine to rats can be described by an open one- or two-compartment model (97). Resveratrol shows a significant cardiac accumulation and a strong affinity for the kidneys and the liver.

Administered in red wine, resveratrol is quickly distributed in the blood stream and can be detected in significant concentrations in the blood and a number of organs (98). After a single oral dose of 4 ml red wine containing 26 µg resveratrol, a 10^{-4} molar concentration is achieved in the liver and the kidneys of rats for >2 h. From a comparison of the dosages considered as active *in vitro* and *in vivo* with the results of plasma and tissue concentrations after single or prolonged administrations of red wine with a known resveratrol content, it can be concluded that the long term oral administration of resveratrol may be sufficient for a beneficial effect on health (99). Moreover, a platelet aggregation test has confirmed that modest dosages of resveratrol could have a pharmacological effect.

The absorption and metabolization of resveratrol by the jejunum in an isolated rat small intestine model were recently studied (100). It was observed that resveratrol is glucuronized during its transfer across the jejunum and is most likely in the form of a glucuronide conjugate when it enters the blood stream. Other experiments on the same model also detected small amounts of resveratrol sulfate on both the luminal and the vascular side of the jejunum (101).

Conclusion

Once absorbed, a chemopreventive agent can operate via different mechanisms, such as the inhibition of the metabolic activation of carcinogenic compounds, the stimulation of reactive metabolite detoxification, the prevention of their interaction with cell DNA and the suppression of tumor progression (102). Resveratrol is able to act on each of these mechanisms. Through inhibiting the activity of the COX-1 and COX-2 enzymes and the cytochrome P450 complex and inducing quinone reductase, resveratrol can simultaneously inhibit promutagen bioactivation, stimulate carcinogen detoxification and prevent the organism against the adverse effects of diverse environmental toxicants. Through inhibiting prostaglandins and NO formation, it can prevent their stimulative effect on tumour development. The causes and development of malignancy also involve the generation of oxygen-reactive species able to damage the major components of cells. Antioxidant derivatives such as resveratrol can fight these processes.

In vitro, *ex vivo* and *in vivo* experiments have demonstrated that, beside its ability to act on each of the previously described chemopreventive mechanisms, resveratrol may also possess a chemotherapeutic potential. Indeed, resveratrol suppresses growth of various cancer cell lines, partly by an inhibition of DNA polymerase and ribonucleotide reductase and partly by inducing cell cycle arrest or apoptosis. Intraperitoneal injections also decrease the number of tumour cells in a Yoshida AH-130 ascite hepatoma rat model.

However, opposing results and controversies involving the available data still remain and call for complementary experiments. *In vivo* results do not always agree with *in vitro* observations. The pleiotropic agent resveratrol is able to significantly interact with numerous biochemical processes. Therefore its activity can not be resumed in a unique mechanism of action but rather seems to result from various complementary actions on different biochemical pathways.

Long-term epidemiological studies on humans will determine the real preventive and therapeutic efficiency of dietary or supplemented resveratrol on tumour development.

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