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Invited paper for Agro Food industry hi-tech

Nutritional prevention by dietary resveratrol as chemopreventive agent: application to colorectal cancers.

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Running title: chemoprevention by resveratrol

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Abbreviations: COX, cyclooxygenase; **NFκB**, nuclear factor kappa B.

Keywords: Resveratrol, cancer, chemoprevention, sensitization.

Abstract

Resveratrol (3,4',5 tri-hydroxystilbene) is a plant phytoalexin produced in massive amount in grapevine skin in response to stress such as UV, phytosanitary treatment, and mostly following infection by *Bothrytis cinerea*. In this later case, the production of resveratrol inhibits the proliferation of the pathogen, thereby acting as a natural antifungal.

Many experimental studies have reported interesting properties of *trans*-resveratrol as a preventive agent against important pathologies i.e. vascular diseases, cancers, viral infection or neurodegenerative processes. In addition, several epidemiological studies indicated that resveratrol would be the main microcomponent of wine leading health benefits such as prevention of vaso-coronary diseases and cancer (so called the "French paradox").

Resveratrol prevent (or delay) carcinogenesis by inhibiting the three phases of cancer process: initiation, promotion, progression and invasion phases. It also exhibits pro-apoptotic properties especially towards colorectal cancers. Importantly, resveratrol is not toxic in animal models even at high dosage. Moreover, plasmatic concentrations of resveratrol would be sufficient for anti-invasive activity. The enterohepatic blood recirculation contributes to a delayed elimination of the molecule from the body which can also show a prolonged effect enhanced by its binding to plasmatic proteins. Interestingly resveratrol can sensitize to low doses of cytotoxic drugs and so provide new approaches to enhance the efficacy of anticancer therapy in human cancers.

INTRODUCTION

1) Resveratrol : a plant phytoalexin

Resveratrol or 3, 4', 5 tri-hydroxystilbene (Figure 1) is a secondary metabolite produced in limited plant species (1). Phenylalanine is the precursor and the key enzyme is the stilbene synthase which orientates the synthesis pathway towards resveratrol, instead of towards flavonoids which involves the chalcone synthase (2). Several plant species are known to produce resveratrol (especially the *trans* isomers such as aglycone or in a glycosylated form), in significant to high amounts. Some of them are used as food, i.e. vine plant, peanuts, berries. In the vine plant, *Vitis vinifera*, resveratrol is a phytoalexin, e.g. produced in huge amounts in grape vine skin in response to infection by *Bothrytis cinerea*, leading to a blockage of its proliferation. The mild stress triggered by resveratrol-dependent host pathogen interaction lead to a systemic response conferring an extended protection against other pathogens (3,4). This process is known as xeno-hormesis (5). Obviously, resveratrol appears to be a real natural antibiotic. Interestingly, although other resveratrol producing plants are not used as

dietary preparation, i.e. *Polygonum cuspidatum* or *Yucca schidigera*., extracts of *Polygonum cuspidatum* were already used in ancient Chinese natural medicine for their vaso-relaxing activity, while root extracts of *Yucca schidigera* were known for their anti-mutagen activity. *Veratrum grandiflorum* has been reported to synthesize resveratrol and analogues. By the way, root powder of *Veratrum album* has long been used for at medium altitude in Northern Europe, Asia and Japan to treat rheumatism and nervous diseases. However, *Veratrum album* contains potent toxic alkaloids: the protoveratrin A & B. For review see (6).

2) Resveratrol and prevention of diseases

Like many other plant polyphenols, resveratrol is a potent anti-oxidant and is considered to be a preventive food microcomponent as are the flavonoids and epicatechins of green tea or of cocoa (7). Indeed, numerous studies have reported interesting properties of *trans*-resveratrol as a preventive agent (figure 1) of several important pathologies: vascular diseases, cancers, viral infection, neurodegenerative processes such as Alzheimer (8) and Huntington diseases (9) (for reviews, see (10,11). Resveratrol protects LDL against oxidation (12). In addition, a novel discovery has been reported, showing that resveratrol increases lifespan (13). Moreover, several epidemiological studies (14) revealed that resveratrol may be one of the main wine microcomponents responsible for the health benefits (i.e. against vaso-coronary diseases and cancer mortality) in the case of moderate wine consumption. Moreover, due to its oestrogeno-mimetic properties, resveratrol may protect women against osteoporosis (15). An extensive and up to dated document has been recently published on resveratrol and health (16).

CANCER CHEMOPREVENTIVE PROPERTIES OF RESVERATROL

The antiproliferative effect of resveratrol has been shown in numerous *in vitro* studies, using several cell lines derived from tumors and its anticarcinogenic effects has been demonstrated in several animal models (17,18). As reported in table 1, resveratrol is able to prevent the tumor initiation by scavenging free radicals damaging DNA and by activation of detoxifying enzymes. Resveratrol inhibits also tumor promotion by modulation of polyamines metabolism and tumor progression, by modulation of cell cycle, apoptosis and angiogenesis. Despite efforts to characterize a major resveratrol affinity target, various resveratrol binding proteins have been identified in different biological models: Wang et al.(19), in CWR22v1 prostate cancer cell lines, Lin et al. (20) in MCF7 mammary gland tumor cells or Han et al. (21), in

plasma membrane of rat brain.

1- Resveratrol acts on carcinogenesis by *inhibiting the initiation phase*

Initiation phase of carcinogenesis is linked to DNA alteration (mutation) of a normal cell. The anti-initiation activity of resveratrol is linked to the suppression of the metabolic activation of carcinogens and/or to an increased detoxification via a modulation of the drug-metabolizing enzymes involved either in phase I reactions or in phase II conjugation.

a)- Resveratrol chemoprevention by *ROS scavenging and DNA repair*

The inhibition of P450 enzymes by resveratrol can reduce the reactive activation of molecular oxygen. These antioxidant actions of resveratrol contribute to prevent oxidative DNA damage which plays a pivotal role in the carcinogenic activity of many genotoxic agents (23).

Resveratrol is also able to promote DNA repair by increasing the activity of p53 in various cell lines.

b)- Resveratrol chemoprevention by *induction of detoxification enzymes.*

Resveratrol chemoprevention by inhibition of phase I enzymes would be due to the prevention of metabolic activation of procarcinogens by a competitive inhibition of the aryl hydrocarbon receptor (AhR) (22).

Phase II enzyme induction generally protects tissues and cells from endogen and/or exogen intermediate carcinogens. Resveratrol contributes to metabolic inactivation by inducing UDP glucuronosyltransferase (24), increases glutathione (GSH) levels and the activity of glutathione-S-transferase (GST) glutathione peroxidase (GPX) and glutathione reductase (GR). Resveratrol could activate the phase II detoxifying enzyme gene expression via a modulation of the mitogen-activated protein kinases (MAPK) pathway.

2- Resveratrol acts on carcinogenesis by *inhibiting the promotion and the progression phases*

Resveratrol is also able to antagonize tumor promotion, such as in the DMBA/TPA mouse skin carcinogenesis model (25). The chemopreventive effect of resveratrol at this point of carcinogenesis goes through.....

a)- Resveratrol chemoprevention by *modulating kinase cascade.*

Resveratrol is able to interfere with several kinase cascades. Indeed resveratrol can inhibit the phosphorylation and the activity of PKC (26) and can also modulate MAPK cascade (27). In contrast, resveratrol is shown to activate extracellular-signal-regulated protein kinases (ERKs), p38 kinase and c-Jun NH2-terminal kinases (JNKs) and their phosphorylation (28).

b)- Resveratrol chemoprevention by *inhibition of polyamine synthesis.*

Polyamines affect numerous processes in carcinogenesis such as promotion, progression and invasion. Downregulation of polyamines levels is associated with decreased cell growth, and increased apoptosis. It appears that resveratrol can inhibit polyamine synthesis and increase polyamine catabolism (29).

c)- Resveratrol chemoprevention by *inhibition of lipid mediators synthesis.*

Lipid mediators such as prostaglandins have been shown to be involved in promoting cell proliferation, suppressing immune surveillance, and stimulating tumorigenesis. The synthesis of these products from arachidonic acid can occur via several pathways such as the prostaglandin H synthase, the cyclooxygenase and the lipoxygenase pathways. The cyclooxygenase inhibition by resveratrol prevents the release of cyclooxygenase products such as prostaglandins and thromboxanes (30).

d)- Resveratrol chemoprevention by *inhibition of nitric oxide.*

In endothelial tumoral cells, endothelial NO synthase (eNOS) promote tumoral growth and metastasis by various mechanisms such as the stimulation of tumoral cell migration, invasion, and angiogenesis (31). For example, it has been shown that the increase in inducible NO synthase and in eNOS is correlated with tumoral growth and vascular invasion in human colorectal cancer (32). Resveratrol is also able to inhibit NO generation in activated macrophages by reducing the amount of cytosolic iNOS protein and by inhibiting the activation of NFκB (33).

e)-Resveratrol chemoprevention by *cell cycle arrest.*

Resveratrol, like many cytotoxic agents, affects cell proliferation by disturbing the normal progression of the cell cycle (for review see (34) :

- Resveratrol and arrest in G1 phase. Resveratrol can decrease the levels of cyclin D1, D2 and E.
- Resveratrol and arrest in S phase. Cyclin E mediates entry into S phase, whereas cyclin A

accumulates later during S phase. Biochemical analysis shows that resveratrol induces a significant increase of cyclins A and B1 with an accumulation of cdk1 and cdk2, which are also increased in their inactive phosphorylated forms. Moreover cyclin B1, D1 and cdk4 are downregulated. Reports attribute the S phase arrest to an inhibition of ribonucleotide synthase and DNA synthesis.

- Resveratrol and G2/M-phase arrest. Cyclin B2 is related mainly to the completion of M phase. This cyclin combines with cdk1 to form MPF which plays an important role in the transition from G2 stage to M stage. Biochemical analysis demonstrates that the disruption of G2 phase progression by resveratrol is accompanied by the inactivation of cdk1 and an increase in the tyrosine phosphorylated (inactive) form of cdk1.

f)- Resveratrol chemoprevention by the *induction of cell death*.

Induction of apoptosis in precancerous or malignant cells is considered to be a promising strategy for chemopreventive or chemotherapeutic purposes. The induction of apoptosis triggered by resveratrol has been observed in various cell types through different pathways. Indeed it has been demonstrated that resveratrol is able to activate cell death by the mitochondrial pathway or by the death receptor pathway (35).

g)- Resveratrol and *progression / invasion inhibition*.

Resveratrol can act on the progression which is associated with the evolution of the initiated cells into a biologically malignant cell population. Studies have shown the involvement of arachidonic acid metabolites in tumor cell invasion and metastasis (36). Since resveratrol is a lipoxygenase and cyclooxygenase inhibitor, it inhibits the invasion of rat ascites hepatoma cells (37).

Angiogenesis provides a gateway for tumor cells to enter the circulation and, in the reverse direction, for leukocytes to infiltrate the tumor and provide proteolytic enzymes and chemokines, which facilitate the migration and invasion of tumor cells. Resveratrol can act on angiogenesis through an inhibition of matrix metalloproteinase, (MMP-9), urokinase-type plasminogen activator and adhesion molecules (38). In addition, resveratrol inhibits hypoxia-inducible factor 1 alpha (HIF-1 α) and VEGF expression in human ovarian cancer cells (39).

RESVERATROL AND PROTECTION AGAINST COLORECTAL CANCER

We have previously reported that resveratrol is able to block the proliferation of rat or human

colon and liver cancer cells (40, 41). In colon cells, this blockage is linked to a cell cycle arrest, as shown by the study of cyclins and kinases involved in cell signaling, on the other hand - to an apoptotic process induced via death receptor pathway, independently of their ligands (figure 2). The activation of apoptotic process involved death receptors redistribution into plasmatic membrane lipid rafts which contributes to triggering the proteolytic caspase cascade (42). It appears that resveratrol pretreatment facilitates the formation of a functional DISC at plasma level. The cholesterol sequestering agent nystatin prevents resveratrol-induced death receptor redistribution and cell sensitization to death receptor stimulation, suggesting that resveratrol-induced redistribution of death receptors in lipid rafts is an essential step in its sensitizing effect expression (42). Additionally, we have shown a rapid resveratrol uptake by hepatic tumoral cells, by both passive diffusion process and carrier-mediated mechanism (43). this last one allowing a good cellular absorption of resveratrol despite its strong binding to plasma proteins, particularly to albumin (44).

Our previous results on cell cultures indicate prospects of application to the prevention or to the therapy of colorectal cancers (CRC). Our present studies consist in testing the effects of resveratrol upon heterotrophic tumors. Our preliminary results tend to show a cytostatic and cytolytic action of orally administered resveratrol on rats implanted with colorectal cells. This approach will allow the determination of the efficacy and toxicity thresholds of resveratrol and the characterization of its metabolism, its bioavailability as well as efflux protein implications. Resveratrol-induced tumoral regression will be correlated to cell cycle modifications, apoptosis induction and to component redistribution into membrane microdomains. Moreover, since resveratrol is able to exhibit immunomodulatory properties *in vitro* (45), and it could play a similar role *in vivo* ; so a search for a possible macrophagic and lymphocytic activation in treated animals is pertinent.

Resveratrol, an adjuvant for chemosensitization and radiosensitization

Despite aggressive therapies, resistance of many tumors to established treatment procedures still constitutes a major problem in cancer therapy. The aim is to know if resveratrol can be a good candidate to fight CCRs, used alone or in association, leading therefore to a chemosensitization in chemoresistant colon cancers. We have shown that resveratrol sensitizes colon tumor cells to apoptosis induced by death receptor ligands (42) (table 2). Moreover, we and others have shown that resveratrol is able to sensitive to TRAIL (tumor necrosis factor-related apoptosis-inducing ligand)-induced apoptosis in cancer cells

(46). In neuroblastoma cells, treatment with resveratrol sensitizes these cells to TRAIL-induced apoptosis in the absence of a functional p53 pathway (35). This sensitization involves a cell cycle arrest-mediated survivin depletion and an upregulation of p21 (35). In human colon cancer cells that are resistant to the cytotoxic effect of resveratrol, we have shown that resveratrol sensitizes these tumor cells to TNF, anti-CD95 antibodies and TRAIL-mediated apoptosis and activates a caspase-dependent death pathway that escapes Bcl-2-mediated expression (46).

In other way, for a better knowledge of possible resveratrol applications in human therapy, it would be interesting to study its effect in combination with other classic anticancer drugs, such as 5-Fu, cisplatin.

The use of experimental model of orthotopic colorectal adenocarcinomas will allow a better investigation of resveratrol therapeutic efficacy in colon cancers and an identification of its targets in this type of cancer.

Potential use: Our various approaches will allow us to determine if resveratrol is also a good candidate for the treatment of CRCs and to elucidate its action mechanism on membrane functions, on metabolic targets and on the expression of nuclear factors implicated in colorectal cancer development. These studies will lead to the evaluation of resveratrol anti-cancer potency and the determination of new treatment targets.

A pretreatment with resveratrol prior to ionizing radiation (IR) exposure of resveratrol radiosensitives human cervical tumor cell lines enhances tumor cell killing by IR in a dose-dependent manner (47).

CONCLUSION

Dietary polyphenols is of great interest due to their antioxidative and anticarcinogenic activities. Indeed, polyphenols can have a chemoprotective effect which is the property of pharmacological or natural agents that promote the arrest or regression of a cancer process. Polyphenols such as resveratrol may inhibit carcinogenesis by affecting the molecular events in the initiation, promotion and progression stages (figure 2).

Resveratrol acts on the carcinogenesis process by affecting the three phases: tumor initiation, promotion and progression phases. It appears that resveratrol can prevent metabolic activation, ROS production, adduct formation and stimulate metabolic inactivation. By its ability to block the cell cycle and to induce apoptosis in tumor cells, resveratrol should be an

important natural chemopreventive agent, especially if its targeting to the tissues can be improved. Resveratrol is able to suppress the final steps of carcinogenesis including angiogenesis and metastasis. Interestingly, resveratrol does not present any cytotoxicity in animal models. Moreover, concentrations of resveratrol and / or metabolite(s) in blood seem to be sufficient for anti-invasive activity. It is likely that most of the resveratrol might have been metabolized into compound(s) which preserve anti-oxidative activity but lose anti-proliferative activity. In fact, the highly polar conjugates are generally inactive and are rapidly excreted in the urine and feces. Enterohepatic recirculation, which releases the parent drug into the systemic circulation, may be associated with a delayed elimination of the drug from the body and a prolongation of its effect. By its binding to plasmatic proteins, the effect of resveratrol could be prolonged. Another property of the polyphenol is drug-chemosensitization. It appears that low doses of resveratrol can sensitize to low doses of cytotoxic drugs and so provide a novel strategy to enhance the efficacy of anticancer therapy in various human cancers.

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Legends of figures

Figure 1. Summary of the resveratrol properties as nutritional preventive agent

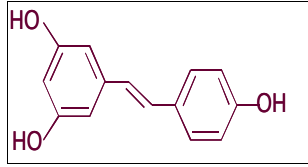
Figure 2. Scheme of resveratrol action modifying equilibrium between gain and loss of cells

Figure 1 : Summary of the dietary resveratrol properties as preventive agent

Anticancer
Antibiotic, antidiabetic, anti-inflammatory,
inhibition of *Helicobacter pylori* growth
Antiviral (Herpes, HIV)

Anti-oxidant, prevention of vascular diseases)
Lifespan increase)
LDL oxidation prevention
Sirtuin activation pathway
Neuroprotection (Alzheimer)
Caloric - restriction mimicking)

Cell growth
(anti tumor effect)
proliferation inhibition
apoptosis
prevention of UV irradiation injury



Human colorectal tumor cell type
Antitumor agent
Sensitive cells (SW480) apoptosis
Resistant cells (HCT116) apoptosis

process

Resveratrol

+

-

Pro-apoptotic agent

-inhibition : polyamines, synthesis, COX-2, MAPKs

+

-down-regulation of transcription factors NFkB, AP-1...

Cytotoxic agent

carcinogen activation, carcinogen deactivation, DNA adduct formation inhibition, DNA

repair activation, , inhibition of polyamine catabolism, inhibition of cell cycle progression,

gap junction inhibition, angiogenesis inhibition, nitric oxide production

Resveratrol + pro-apoptotic agent (or + cytotoxic agent)

+

+

(sensitization (1))

Y. Shan et al (2004 *Biochem Biophys Res Comm* 323 :743-749

4) *Oncogene* 23(8) 845-86J., august issue