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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.

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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-apoptic properties especially towards colorectal cancers. Importantly, resveratrol is not toxic in animal models even at high dosage. Moreover, plasmatic concentrations of resveratrol would to 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 hudge 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 confering 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. Interstingly, 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 rheumatisms and nervous diseases. However, *Veratrum album* contains potent toxic alcaloids: the protoveratrines 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 epicathechins 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 CWR22vl 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-1α) 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 heterotropic 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-chemosenzitisation. 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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References

1. P. Langcake, Pryce, "A new class of phytoalexins from grapevines", *Experientia*, 33, pp151-2 (1977)

2. R. Bessis, "Propriétés du resvératrol" *Vin et Santé* 3, pp 61-73 (1998)

3. M. Iriti et al. " Benzothiadiazole enhances resveratrol and anthocyanin biosynthesis in grapevine, meanwhile improving resistance to Botrytis cinerea", *J Agric Food Chem* 52, pp 4406-13 (2004)

4. A. Aziz et al. " Laminarin elicits defense responses in grapevine and induces protection against Botrytis cinerea and Plasmopara viticola", *Mol Plant Microbiol Interac* 16, pp 1118-28 (2003)

5. JA. Baur, Sinclair DA ," Therapeutic potential of resveratrol: the in vivo evidence" *Nature Drug Discovery*, 5, pp 493-506 (2006)

6. D. Delmas et al., " Resveratrol a protecting agent against vascular alterations and ageing", *Mol Nut Fd Res* 49 pp 377-395 (2005)

7. PM. Kris-Etherton, et al. " Evidence that the antioxidant flavonoids in tea and cocoa are

beneficial for cardiovascular health." *Curr Opin Lipidol*, 13,pp 41-9 (2002)

8. A. Russo, et al., " Red wine micronutrients as protective agents in Alzheimer-like induced insult", *Life Sci*., 72, pp :2369-79 (2003)

9. Y. Surh, " Molecular mechanisms of chemopreventive effects of selected dietary and medicinal phenolic substances", Mutat Res., 428, pp 305-27 (1999

10. N. Latruffe et al., " Molecular analysis on the a chemopreventive properties of resveratrol, a plant polyphenol microcomponent", *Int J Mol Med* 10, pp 755-60 (2002)

11. JA. Parker et al., " Resveratrol rescues mutant polyglutamine cytotoxicity in nematode and mammalian neurons", *Nature genetics* 37, pp 349-50 (2005)

12. D. Blache et al., "Gas chromatographic analysis of resveratrol in plasma, lipoproteins and cells after in vitro incubations", *J Chromatog B Biomed Appl* 702, pp 103-10 (1997)

13. KT. Howitz et al., " Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan", *Nature*, 425, pp 191-6 (2003)

14. SC. Renaud et al., " Alcohol and mortality in middle-aged men from eastern France" *Epidemiology* 9, pp184-8 (1998)

15. D. Bagchi et al., "Benefits of resveratrol in women's health", *Drugs Exp Clin Res*, 27, pp 233-48 (2001)

16. BB. Aggarwal, Shishodia, "Resveratrol in health and diseases", eds pp 475-497, Taylor & Francis, CRC Press, ISBN 0-8493-3371-7

17. M. Jang et al., "Cancer chemopreventive activity of resveratrol, a natural product derived from grapes " , *Science* 275, pp 218-220, 1(997)

18. F. Levi et al., " Resveratrol and breast cancer risk", *Eur J Canc Prev*, 14, pp 139-42 (2005)

19. Z. Wang et al., " Identification and purification of resveratrol targeting proteins using immobilized resveratrol affinity chromatography", *Biochem Biophys Res Commun*., 323, pp 743-9 (2004)

20. HY. Lin et al. "Integrin {alpha}V{beta}3 contains a receptor site for resveratrol", *FASEB J*, 20, E1-E6 august (2006)

21. YS. Han et al., " Specific plasma membrane binding sites for polyphenols, including resveratrol, in the rat brain", *J Pharm Exp Ther*, 318, pp 238-45 (2006)

22. RF. Casper et al., " Resveratrol has antagonist activity on the aryl hydrocarbon receptor: implications for prevention of dioxin toxicity", *Mol Pharmacol* 56, pp 784-790, (1999)

23. SS. Leonard et al., " Resveratrol scavenges reactive oxygen species and effects radical-induced cellular responses", *Biochem Biophys Res Commun* 309, pp1017-26

24. C. Gerhauser et al., " Mechanism-based in vitro screening of potential cancer chemopreventive agents." *Mutat Res* 523-524, pp 163-72

25. M. Jang , Pezzuto JM , " Effects of resveratrol on 12-O-tetradecanoylphorbol-13-acetate-induced oxidative events and gene expression in mouse skin" *Cancer lett*. 134, pp 81-9 (1998)

26. Z. Wang et al., " *Biochem Biophys Res Commun* 323, pp 743-9 (2004)

Wang Z, Li Y, Liu ET, Yu Q. Related Articles, Links [Abstract] Susceptibility to cell death induced by blockade of MAPK pathway in human colorectal cancer cells carrying Ras mutations is dependent on p53 status.

Biochem Biophys Res Commun. 2004 Sep 17;322(2):609-13.

27. SK. Manna et al., " Resveratrol suppresses TNF-induced activation of nuclear transcription factors NF-kappa B, activator protein-1, and apoptosis: potential role of reactive oxygen intermediates and lipid peroxidation"' *J. Immunol* 164, pp 6509-19 (2000)

28. RM. Niles et al., " Resveratrol is a potent inducer of apoptosis in human melanoma cells" *Cancer Lett* 109, pp 157-163 (2003)

29. F. Wolter et al., " Resveratrol-induced modification of polyamine metabolism is accompanied by induction of c-Fos", *Carcinogenesis*, 24, pp 469-74 (2003)

30. J. Knight et al., " Eicosanoid biosynthesis in an advanced deuterostomate invertebrate, the sea squirt (Ciona intestinalis)", .*Biochim Biophys Acta* 1436, pp 467-78 (1999)

31. N. Yagihashi et al., " Increased in situ expression of nitric oxide synthase in human colorectal cancer", *Virchows Arch* 436, pp 109-14 (2000)

32. S-H. Tsai et al., " Suppression of nitric oxide synthase and the down-regulation of the activation of NFkappaB in macrophages by resveratrol", *Br J Pharmacol* 126, pp 673-80 (1999)

33. Banerjee S et al., " Suppression of 7,12-dimethylbenz(a)anthracene-induced mammary carcinogenesis in rats by resveratrol: role of nuclear factor-kappaB, cyclooxygenase 2, and matrix metalloprotease 9", *Cancer Res* 62, pp 4945-4954 (2002)

34. D. Delmas et al., "Resveratrol as chemopreventive agent : new concepts to put forward the molecule to fight cancer", *Curr Drug Targ* 7, pp 423-42 (2006)

35. S. Fulda, Debatin K, " Sensitization for tumor necrosis factor-related apoptosis-inducing ligand-induced apoptosis by the chemopreventive agent resveratrol", *Cancer Res* 64, pp 337-346 (2004)

36. R. Reich, Martin GR., " Identification of arachidonic acid pathways required for the invasive and metastatic activity of malignant tumor cells", *Prostaglandins* 51, pp 1-17 (1996)

Plant Physiopathology
(phytoalexin dependent –
defense mechanism)
Antifungal
Xeno-hormesis

37. Maccarrone et al., " Resveratrol prevents apoptosis in K562 cells by inhibiting lipoxygenase and cyclooxygenase activity", *Eur J Biochem*. 265, pp 27-34 (1999)

38. BB. Aggarwal et al., " From chemoprevention to chemotherapy: common targets and common goals", *Expert Opin Investig Drugs* 13: 1327-8 (2004)

39. Z. Cao et al., " trans-3,4,5'-Trihydroxystibene inhibits hypoxia-inducible factor 1alpha and vascular endothelial growth factor expression in human ovarian cancer cells" *Clin Cancer Res* 10: 5253-63 (2004)

40. D. Delmas et al., " Inhibitory effect of resveratrol on the proliferation of human and hepatic derived cell lines", *Oncol Rep* 7, pp 847-52 (2000)

41. D. Delmas et al. " Resveratrol, a chemopreventive agent, disrupts the cell cycle control of human SW480 colorectal tumor cells", *Int J Mol Biol*, 10, pp 193-9 (2002)

42. D. Delmas et al., " Resveratrol-induced apoptosis is associated with Fas redistribution in the rafts and the formation of a death inducing signaling complex in colon cancer cells *", J Biol Chem*, 278, 41482-90 (2003)

43. A. Lançon et al., " Human hepatic cell uptake of resveratrol: involvement of both passive diffusion and carrier-mediated process", *Biochem Biophys Res Commun* **316**, pp 1132-7 (2004)

1) B. Jannin et al., " Transport of resveratrol, a cancer chemopreventive agent, to cellular targets, plasmatic protein binding and cell uptake", *Biochem. Pharmacol*., 68, pp 1113-1118 (2004)
2) GY Kim et al., Resveratrol inhibits phenotypic and functional maturation of murine bone marrow-derived dendritic cells", *Int Immunopharmacol* 2, pp 245-53 (2004)

46. D. Delmas et al., " Redistribution of CD95, DR4 and DR5 in rafts accounts for the synergistic toxicity of resveratrol and death receptors ligands in colon carcinoma cells", *Oncogene*, 23, pp 8979-86 (2004)

47. I. Zoberi et al., " Radiosensitizing and anti-proliferative effects of resveratrol in two human cervical tumor cell lines**",** *Cancer Lett* , 175:165-73 (2002)

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

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

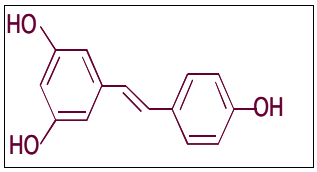
IHos

biotic, antiseptic, anti-inflammatory)
tion of *Helicobacter pylori* growth
viral (Herpes, HIV)

s

(anti oxidant, *prevention of vascular diseases*)
LDL oxidation prevention
Neuprotection (Alzheimer)
(*lifespan increase*)
Sirtuin activation pathway
Caloric – restriction mimicking)

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



stic effect of resveratrol with pro-apoptotic or cytotoxic agents in the apoptotic

Human colorectal tumor cell type

Antitumor agent

Sensitive cells (SW480) apotosis

Resistant cells (HCT116) apoptosis

Resveratrol

+

-

Pro-apoptotic agent

TRAIL, ONYX

+

-

Cytotoxic agent

5FU

+

-

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

+

+

(sensitization (1)

-ibition : polyamines synthesis, COX-2, MAPKs

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

carcinogen activation, carcinogen desactivation, DNA adduct formation inhibition, DNA repair activation, , inhibition of polyamine catabolism, inhibition of cell cycle progression, gap junction inhibition, angiogenesis inhibition, nitric oxide production

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

H.Y. Lin (2006) *FASEB J.*, august issue

4) *Oncogene* 23: 8979-86