RESEARCH ARTICLE

REDUCTION OF HEPATOTOXICITY INDUCED BY DOXORUBICIN

[1,2,3,*]Dorsaf Bengaied, [4]Antonio RIBEIRO, [3]Mohamed Amri, [1]Daniel scherman and [1,2]Philippe Arnaud

[1]Chemical, Genetic and Imaging Pharmacology Laboratory, Faculty of Pharmacy, Chimie ParisTech, Paris Descartes University, Sorbonne Paris Cite, INSERM U1022, CNRS UMR8151, 4 Avenue de l'Observatoire, ´75006 Paris, France
[2]Galenic Laboratory, Faculty of Pharmacy, Paris, France
[3]Laboratory of Functional Neurophysiology and Pathology, Research Unit UR/11ES09, Department of Biological Sciences, Faculty of Science of Tunis, University Tunis El Manar, Tunis, Tunisia
[4]Faculty of Pharmacy of University of Coimbra

ABSTRACT

Doxorubicin (DOX) has been used in the treatment of variety of cancers but its administration is limited by a dose-dependent toxicity. Its cytotoxic effects on malignant cells, have shown an increase in the risk of cardiotoxicity, hepatoxicity, renal insufisance. Antioxydants have been explored for both their cancer preventive properties and chemodulatory of DOX toxicity. Resveratrol (RSV) is a polyphenolic constituent of several dietary mainly of grapes and wine origin recently its anti-cancer potential has been extensively explored, revealing its anti-proliferative effect on different cancer cell lines, both *in vitro* and *in vivo*. RSV is also known to have modulatory effects on cell apoptosis, migration and growth via various signaling pathways. Though, RSV possesses great medicinal value, its applications as a therapeutic drug are limited. Problems like low oral bioavailability and poor aqueous solubility make RSV an unreliable candidate for therapeutic purposes. Additionally, the rapid gastrointestinal digestion of RSV is also a major barrier for its clinical translation. Hence, to overcome these disadvantages RSV-based nanodelivery systems have been considered in recent times. Nanodelivery systems of RSV have shown promising results in its uptake by the epithelial system as well as enhanced delivery to the target site. Herein we have tried to bring new new insights into the molecular mechanisms of DOX toxicity with respect to DNA damage, free radicals and whether RSV can be a playmaker as chemomodulatory of DOX

INTRODUCTION

Doxorubicin (DOX) is an anthracycline, also known as Adriamycin, has been used in oncologic practice since the late 1960s. It can be contributed as a simple agent or in association with other chemotherapeutic drug in the treatment of cancers, including leukemias, lymphomas, and solid tumors, but its administration is limited by a dose-dependent, irreversible, and progressive toxicity.

Corresponding author: [1,2,3,*]Dorsaf Bengaied
[1]Chemical, Genetic and Imaging Pharmacology Laboratory, Faculty of Pharmacy, Chimie ParisTech, Paris Descartes University, Sorbonne Paris Cite, INSERM U1022, CNRS UMR8151, 4 Avenue de l'Observatoire, ´75006 Paris, France
[2]Galenic Laboratory, Faculty of Pharmacy, Paris, France
[3]Laboratory of Functional Neurophysiology and Pathology, Research Unit UR/11ES09, Department of Biological Sciences, Faculty of Science of Tunis, University Tunis El Manar, Tunis, Tunisia

The benefit of cytotoxic effects on malignant cells is hampered by the risk of cardiotoxicity, hepatoxicity, renal insufficiency (Buzdar *et al.* 1985). Hepatic dysfunction occasionally necessitates the withdrawal of or dose adjustments to not only DOX but also the coadministered medicines used to treat disease complications and improve unpleasant symptoms, thereby increasing the risk for chemotherapy failure (Nagai *et al.*, 2016). Therefore, it is considered to be of critical importance to explore strategies for reducing the incidence and severity of the hepatic toxicity of anthracyclines. Changes in the expression and activity of various biomolecules have been regarded as a likely mechanism for the cardiotoxicity of DOX (Nagai *et al.* 2016). In contrast, oxidative stress is generally considered to be a major cause of DOX hepatotoxicity(Kassner *et al.* 2008); However, the mechanisms underlying DOX-induced hepatic impairments have not yet been elucidated in detail. It has been reported that the extrinsic and intrinsic apoptotic responses mediated by Fas and Bax, respectively,

were both associated with DOX-induced acute hepatic damage (Kassner *et al.* 2008), which may be helpful for establishing a rational strategy to alleviate organ toxicity. Resveratrol (3,4′,5-trihydroxy-trans-stilbene) is a polyphenol of the stilbene classfound in some fruits such as grapes, blackberries or peanuts. His name would come fromVeratrum's album L. var grandiflorum, the white verrato, from which it was first extracted in1939 by Takaoka in Japan. It was also identified in 1959 in a eucalyptus and then in 1963 inthe root of Fallopia japonica (or Polygonum cuspidatum) (Aggarwal *et al.* 2005).Resveratrol is a good candidate for the use of the French paradox, anexpression that refers to the surprising situation that in the south-western European region, in spite of a highanimal fats food intake, a lower cardiovascular disease is observed when comparing to northern European countries. Resveratrol (RSV) is a phytoalexin (antimicrobial) and it has been discovered that it has many beneficial effects. Apart from the prevention of coronary artery disease, the list of its well-documented beneficial effects has continued to grow : it involves inflammation, platelet activation, angiogenesis, maintenance of bone mass, reduction of adipose mass, neuroprotection, photoprotection, anti-tumorigenic, cardioprotective, anti-aging and antiviral effects(Goswami et Das 2009). The RSV activities are mediated by the modulation of several molecules of cell signaling regulating cell cycle progression, inflammation, proliferation, apoptosis, invasion, metastasis and angiogenesis of tumor cells (Aggarwal *et al.* 2004), (Shakibaei, Harikumar, et Aggarwal 2009), (Lin *et al.* 2016)It has been prouved that RSV can sensitize resistant cells to chemotherapeutic agents by overcoming one or more mechanisms of chemoresistance. In some tumor cells, however, RSV has been shown to act as chemoprotector. The potentialmechanisms underlying this dual effect are described in this review. Berberine is an alkaloid extracted from coptis, cork and other traditional Chinesemedicines that possesses a broad spectrum of pharmacological and therapeutic activités. The protective effect ofberberine against DOX was also evaluated in the liver by histopathology (Pradeep *et al.* 2007).

Doxorubicin

Mechanism of action and anticancer cytotoxicity

Doxorubicin (DOX) like other anthracyclines, is a DNA intercalating agent. Furthermore these molecules are inhibitors oftype II DNA topoisomerases, enzymes involved in the maintenance of the three dimensionalstructure of the DNA during transcription and of the phenomena of replication [10]. ComplexDNA /topoisomerase strands are stabilized thereby preventing DNA replication (Lefrak *et al.* 1973). DOX provokes a drastic oxidative-stress status within erythrocytes and plasma, asassessed by high malondialdehyde (MDA) and carbonyl protein, elevated aspartateaminotransferase (AST) and alanine aminotransferase (ALT) within plasma, and a drasticdepression in some of the antioxidant enzymes in both compartments [11]. DOX also increasesfree iron and H_2O_2 and depressed Ca^{2+} within erythrocytes as well as into plasma and it likelyinduces the highly toxic hydroxyl radical which in turn affected Ca^{2+} homeostasis (Hamlaoui *et al.* 2012).

Doxorubicin-induced cardiotoxicity and hepatotoxicity

Dose effect of DOX show different effects among types of cancer disease. Besides, the administration time length is also important (Aikemu *et al.* 2016). Two ways of free radical formation by DOX have been demonstrated (Pereira-Caro *et*

al. 2011).The first pathway causes the formation of a free radical of semiquinone by the formation of several semi-inhibitors of DOX. In the presence of oxygen, redox cycling of DOX-derived quinone– semiquinone yields superoxide radicals (Quiles *et al.* 2002). In the second pathway, the DOX free radicals originate from a non-enzymatic mechanism involving reactions with iron. For example, Fe^{3+} reacts with DOX in a redox reaction after which the iron atom accepts an electron and a Fe^{2+} DOX free radical complex is produced. This iron–DOX complex can reduce oxygen to hydrogen peroxide and other active oxygen species (Quiles *et al.* 2002). DOX generate superoxide anion radicals, H_2O_2 and hydroxyl radicals as a result of oxidative metabolism in rats (Doroshow 1983). Oxygen-free radicals produced during the metabolic activation of DOX may have toxic effects on heart muscle (Hamlaoui *et al.* 2012), which is provided with poor mechanisms of detoxification of this muscle. The DOX is likely to have toxic effects on liver (Montgomery *et al.* 2017) by increasing levels of superoxidedismutase (SOD), catalase (CAT) and glutathione peroxidase (GSHPx) enzyme in guinea pigs liver tissue(S. Zhang *et al.* 2010). Nevertheless, distrubition of a unique dose of DOX decreases the contentof cytochrome P-450 and glutathione in rat liver (Marchand et Renton 1981)and high glutathione levels have beenfound to protect isolated hepatocytes from DOX toxicity (Zhou *et al.* 2015).

Delivery systems for Doxorubicin

Effect of delivery systems on pharmacokinetics and biodistribution

The pharmacokinetic studies of DOX have shown that doxorubicin effect results is made up of several phases after intravenous injection, whereas intravenous infusion is often followed by three phase plasma clearance. The administration of DOX is 3 to 5 minutes, shows the rapid absorption of the drug by the cells. It is the terminal half-life of 24 to 36 h. This shows to remove the tissue from its absorption (Zheng *et al.* 2006). An equilibrium distribution of the drug is unavoidable to reduce the risk of toxicity. The range of constant distribution varies from 500 to 800 l / m2,allowing body tissues to take up a sufficient amount of doxorubicin (Zheng *et al.* 2006). DOX binds to plasma proteins and most drugs, DOX enters the cell by passive diffusion, general accumulating at intracellular concentrations (Tacar, Sriamornsak, et Dass 2013). Doxorubicin acts in a non-specific manner, acting on normal cells. Which proves the side effects in the cancer patient due to DOX unpredictable cytotoxic properties. Several studies have been carried out to develop specific DOX distribution systemscapable of reducing their toxicity to target its effects directly on tumor cells. The use of thesedrug delivery systems is constantly tested and improved to increase the efficacy, selectivity andtotal effect of antineoplastic drugs. As we can see in table I, most promising DOX delivery systems include the entrapment of the chemotherapeutic drug into polymeric drug carriers, such as liposomes, and nanoparticles (Tacar, Sriamornsak, et Dass 2013).

Liposomal

Doxil® (doxorubicin HCl liposome injection [PLD]); distributed in the United States by Tibotec Therapeutics, a division of Ortho Biotech Products, L.P., Bridgewater, NJ; Caelyx®is distributed outside the United States by Schering-

Plough, Kenilworth, NJ) It isdoxorubicin encapsulated in a pegylated liposome composed of hydrogenated soy phosphatidylcholine, N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (mPEG-DSPE), and cholesterol(Udhrain, Skubitz, et Northfelt 2007). Doxorubicinisis loaded into liposomes at a high concentration under the influence of an ammonium sulfategradient and is suspended in a non-electrolytic solution (Haran *et al.* 1993). Each liposome contains 9,000 to 16,000 molecules of doxorubicin. More than 91% of the drug is encapsulated in the liposomes (Udhrain, Skubitz, et Northfelt 2007). The liposomes are 80 to 100 nm in diameter, with linear segments of surface-grafted PEGextending in a brush formation about 5 to 6 nm from the surface(Lasic *et al.* 1991).

In pegylated liposomal DOX (PLD), release of DOX from the carrier is slow (half-life is several days). Because the DOX stays associated with the carrier, it has pharmacokinetics similar to that of the carrier, which results in significantly altered plasma pharmacokinetics for PLD when compared with conventional DOX. This includes significantly higher area under the plasma-concentration-time curve (AUC), increased distribution half-life, lower rate of clearance, smaller volume of distribution, and 15- to 40-fold higher peak concentrations(Di Lorenzo *et al.* 2007), (Matsumura *et al.* 2004),(Allen 1998).

formulated in a variety of sizes(Lasic *et al.* 1991). The PEG coating on pegylated liposomes is the unique feature thatdistinguishes them from conventional liposomes. In addition to preventing opsonization byplasma proteins, leading to reduced RES uptake of liposomes, PEG provides A steric stabilizingeffect that results in reduced binding to cells, blood vessel walls and other surfaces. The sterictabilization effect leads to the reported colloidal stability for pegylated liposome suspensions. The DOX-loaded PLD do not aggregate or out of suspension over a 2-year period. These sterilestabilized liposomes can circulate for several hours and, if they are very small, pass through thecapillariesthat have increased permeability, such as capillaries in diseased tissues or in the liverand certain other organs. Such long-circulating liposomes distribute as intact particles to normaltissues as well, perhaps by a process of transcytosis and/or extravasation at the level of postcapillary venules (Working *et al.* 1999). The liposomes are slowly removed from circulation by acombination of RES uptake and extravasation in normal tissues(Working *et al.* 1999).

Nanoparticle

In the past, polymers such as dextran and polyethyleneimine have been used as potential chemotherapeutic delivery carriers (Table I).

Table 1. Composition of delivery systems for DOX

Delivery system	Purpose	Output	References
Dextran−doxorubicin (Dex−DOX) conjugate.	Antitumor efficacy.	A higher molecular weight endowed the Dex−DOX conjugate with a better antitumor efficacy in a limited number of tested samples. (In vitro)	(Z. Liu et al. 2017)
Zincoxide nanoparticles (n-ZnO)	Antitumor efficacy	Blends of the nanocrystalline zinc oxide nanoparticles (n-ZnO) and triblock copolymer treated from the solution have been used to make the hybrid polymer-metal oxide for the preparation of the drug loaded nanocomposite.	(Ahmadkhani et al. 2017)
Gold nanoparticles	Anti-cancer efficacy.	Delivery of three cytotoxic drugs with a newly designed PEGylated gold NPs may provide promising and novel prospect in cancer therapy.	(Ghorbani et Hamishehkar 2017)
Polyethylene sebacate (PES)-Gantrez® AN 119 Dox NPs	Anti-cancer efficacy.	The high efficacy coupled with greater safety portrayed Pul Dox NPs as a promising nanocarrier for improved therapy of HCC.	(Pranatharthiharan et al. 2017)
Porous Silicon Nanoparticles	Inhibition of Doxorubicin-Resistant Cancer Cells.	A synergistic effect with the presence of AmQu is observed in both normal MCF-7 and DOX-resistant MCF-7 breast cancer cells.	(Z. Liu et al. 2017)
Doxorubicin loaded Galactose conjugated poly(d,l-lactide-co-glycolide)(PLGA) nanoparticles.	Hepatocyte-targeting drug Carrier.	Cell cytotoxicity tests showed that unloaded NPs are non-toxic and that doxorubicin-loaded NPs caused a cellular viability decrease of around 80%, therefore representing a promising approach to improve liver-specific drug delivery.	(Margarida Cardoso et al. 2016)
Poly(ethylene glycol)-b-poly(L-lactide-co-2-methyl-2(2-dicarba-closo-dodecarborane) propyloxycarbonyl-propyne carbonate) (PLMB)	Anti-cancer efficacy.	It was demonstrated that DOX@PLMB nanoparticles could selectively deliver boron atoms and DOX to the tumor site simultaneously in vivo	(Xiong et al. 2015)
Dextran−doxorubicin (Dex−DOX) conjugate.	Antitumor efficacy.	The in vivo efficacy of these nanoparticles as antitumor drug carriers, was determined by tumor regression and increased survival time as compared to drug conjugate and free drug.	(Mitra et al. 2001)

Tissue concentrations of DOX are also significantly higher, and remain higher for significantly longer periods of time following delivery via pegylated liposomes, as compared withfree drug. Alterations in the pharmacokinetics and biodistribution of DOX, when delivered inpegylated liposomes, reduce cardiotoxicity and myelotoxicity and, increase drug efficacy(Working *et al.* 1999).By comparison, non-pegylated liposomal doxorubicin (NPLD) is approximately 160 nm in diameter,(Cowens *et al.* 1993) although both pegylated andconventional liposomes may be

Antitumour efficacy of Dextran−doxorubicin (Dex−DOX) conjugate increased with the molecular weight of dextran (Z. Liu *et al.* 2017). Blends of the nanocrystalline zinc oxide nanoparticles (n-ZnO) And a copolymer consisting of three blocks was used to form the polymer-hybrid metal oxide for the preparationof DOX loaded nanocomposite (Ahmadkhani *et al.* 2017). Pegylated gold nanoparticles (NPs) have been delivered DOX successfully with anti-cancer efficacy (Ghorbani et Hamishehkar 2017). DOX was encapsulated into polyethylene sebacate (PES)-Gantrez® AN

119 NPs andits high efficacy coupled with greater safety portrayed those NPs as a promising carrier for improved therapy of HCC (Pranatharthiharan *et al.* 2017). DOX-loaded galactose-conjugated poly(d,l-lactide-co-glycolide) (PLGA) NPS aimed at targeting hepatocytes revealed that unloaded NPs are non-toxic while DOX-loaded NPs caused a cellular viability decrease of around 80% (Margarida Cardoso *et al.* 2016). Poly(ethylene glycol)-b-poly(L-lactide-co-2-methyl-2(2-dicarba-closo-dodecarborane) propyloxycarbonyl-propyne carbonate) (DOX@PLMB) NPs could selectively deliver boron atoms and DOX to the tumor site simultaneously in vivo (Xiong *et al.* 2015). When the MG-63 and SaOS-2 cell lines were treated with the dextran-DOX-PEI nanoparticles, the cell numbers were reduced from 5 to 10% at a concentration of 1 to 10 mg / l relative to free doxorubicin on 24 -48 h(Tan *et al.* 2010). Also, the cytotoxicity may be reduced due to slow-coupled DOX release from the nanoparticles. These DOX-coupled nanoparticles also showed selective delivery to tumours. This increases the margin of safety as well as reduces side-effects associated with DOX-loaded dextran-PEI nanoparticles. The avantage of nanoparticles asa drug delivery system is that they can be manufactured with ease, with the added benefits of low cytotoxicity and biodegradable properties. A recent study implicated the encapsulation of DOX using a chitosan drug delivery system by the complex coacervation process with dextran sulfate(Tan *et al.* 2010).A level of encapsulation of more than 99% has been achieved, andthe study prouved that osteosarcoma cell death with thesenanoparticles occurred through apoptosis, necrosis andautophagic cell death. Treatment with doxorubicin nanoparticles in mice having orthotopic osteosarcoma reduced tumor growth, decreased tumor-associated osteolysis and reduced metastasis to the lungs. These nanoparticlesdid not cause side effects in mice – specifically to theheart or skin. Doxorubicinnnanoparticles may prove to be useful clinically provided further studies are performed to validate such formulations in clinically relevant animal tumour models (Mitra *et al.* 2001).

Antioxidants as drugs decreasing toxicity-resveratrol

Antioxydants

Antioxydants have been explored for both their cancer preventive properties and chemodulatory effect on of DOX toxicity. In many studies Vitamin E neutralizes lipid peroxidation and unsaturated membrane lipids because of its oxygen scavenging effect (Quiles *et al.* 2002) and (S. Kalender *et al.* 2004). But some investigators have previously stated these effects of vitamin E have been found at 200 mg/kg/day dose levels (Kozluca *et al.* 1996) and (S. Kalender *et al.* 2004). Vitamin E protects cells and subcellular structures from the oxidative damage by decreasingMultiple displacement amplification (MDA) levels. There were no toxic effects of vitamin E on prescribed doses. Vitamin E was shown to decrease MDA level or keep its original value while increase SOD, GSHPx and CAT enzyme levels or keeping their original value. This shows that vitamin E used single oxygen formation pathway. Vitamin E alone or in combination with DOX treatment may inhibit the toxic and hepatotoxic effects of DOX (Y. Kalender, Y el, et Kalender 2005). Dose and time schedules of treatmentwith catechin, a flavan-3-ol, a type of natural phenol and antioxidantwere chosen so that high levels of scavenging activities were met during early stages of the presence of DOX in the cells. Additionally, in vitro

experiments on an iron loaded rat heart impairment model which was made atonous helped them to select dose of catechin because high and long-term catechin therapy caused toxic effects on cardiac cells (Kozluca *et al.* 1996). Recent studies proved that the antioxidant effect of catechin was related to the free radical scavenging activity (Kozluca *et al.* 1996)and (Hodnick *et al.* 1986). the catechin caused an increase in the levels of, CAT, GSHPx and SOD enzymes. In the same way, catechin with DXR also caused a slight increase in these enzymes.(Y. Kalender, Yel, et Kalender 2005)

Resveratrol

Several in vitro and in vivostudies have shown the potential role of RSV as a anti tumoral hepatic agent. These studies are summarized in Table II. In hepatocellular carcinoma cells (HCC) RSV reduced hexokinase 2, which provides a new dimension to clinical HCC therapies aimed at preventing disease progression. In some studies in which RSV was tested in association with other compounds in HepG2 cells, RSV revealed anticancer potential for liver. In vivo hepatotoxicity studies performed in BALB/c mice revealed that RSV could be useful for the treatment of hepatoxicity induced by oxaldiplatin (Schwingel *et al.* 2014) whilst in vitro cytotoxic effects of RSV showed that phytoallexin exerts differential effect with etoposide on proliferation of cancer cells which is mainly accompanied by p53 activation(Amiri *et al.* 2013). The differentiation of human hepatoblastoma HepG2 cells and ao rat hepatoma were negatively impacted by the addition of RSV to the culture medium in both dose and time-dependent manner (D. Delmas *et al.* 2000). The polyphenolic compound is increasing the number of cells arrested in the S and G2/M phase and likely delay or to prevent the cells from entering mitosis (D. Delmas *et al.* 2000). Hepatic growth factor (HGF) has been implicated in the ability of primary hepatic tumors to proliferate and invade adjacent tissue (D. Delmas *et al.* 2000). The effects of RSV on Hepatic growth factor mediated invasion determined in HepG2 cells, revealed that RSV decreased invasion of liver cancer cells and hepatic growth factor induced scattering with concurrent inhibition of cell proliferation possibly due to a post-receptor mechanism rather than apoptosis (D. Delmas *et al.* 2000).

Resveratrol inhibited both invasion of AH109A rat ascites hepatoma cells and the proliferation at higher concentrations but suppressed only the invasion at lower concentrations, and that RSV-loaded rat serum restrained only the invasion, which suggested that antiinvasive activity of RSV is independent of its antiproliferative activity but a relationship to its antioxidative property was found (Kozuki, Miura, et Yagasaki 2001). Subsequent studies confirmed the implication of the antioxidant property of RSV as sera from rats orally given RSV were found to suppress ROS potentiated invasion of AH109A cells(Miura, Miura, et Yagasaki 2004). Another study focused on factors involved in angiogenesis of expanding tumors proposed a mechanism of RSV's ability to curtail hepatoma cell invasion hails (Kuo, Chiang, et Lin 2002). Although it had been known RSV had antiangiogenic abilities, it was found that RSV had an inhibitory effect on vascular endothelial growth factor gene expression via hypoxia-inducible factor-1a inhibition (Q. Zhang *et al.* 2005). Kuo *et al* (Kuo, Chiang, et Lin 2002). The results proved that RSV inhibited cell growth only in p53- positive HepG2 cells, which was a result of cellular apoptotic death via p53 dependent pathway. It was shown that RSV treated cells were

arrested in G1 phase and were associated with an increase in p21 and expression. The cytotoxic effects of RSV in HepG2 cells were confirmed by Kim *et al* (Kim *et al.* 2002), who isolated the stilbene from the seeds of Paeonia lactiflora, a plant widely used in Chinese traditional medicine. An observation regarding time-dependent and concentration effects of RSV on cytotoxicity, apoptosis and cell proliferation activity in HepG2 cells has been reported (Kocsis *et al.* 2005). Cytotoxicity became evident at RSV concentration of 50 or 100 μM at treatments longer than 48 h. Cell cycle analysis showed an increase of Sphase cells at low concentrations of RSV (10–50 μM) and a decrease at high concentrations (100–200 μM). The synergistic antitumor effects of RSV with current anticancer drug 5-fluorouracil (5-FU) increased to a greater extent than for H22 cells exposed to 5-FU alone. A direct evidence of apoptosis was presented as the mechanism of antihepatoma activity of RSV(Kocsis *et al.* 2005). Another study has found the time- and dose-dependent effects of RSV on cell proliferation in HepG2 cell lines (Stervbo, Vang, et Bonnesen 2006).

General resveratrol pharmacokinetics

The RSV pharmacokinetics have also been investigated in preclinical models as well as in humans (Dominique Delmas *et al.* 2006)(Baur et Sinclair 2006).

Absorption and Bioavailability

This polyphenol has high oral absorption but extensive and rapid metabolism without adverse effects in both rodents (A. A. Bertelli *et al.* 1996), (Niles *et al.* 2006) and humans (Goldberg, Yan, et Soleas 2003), (Das et Ng 2011). In humans, about 70 % of orally administered RSV (25 mg) is rapidly (< 30 min) absorbed and metabolized with a peak plasma level of ≈ 2 μM of RSV metabolites and a half-life of 9-10 h (Goldberg, Yan, et Soleas 2003) (Walle *et al.* 2004), (Yin *et al.* 2016). The extent to which the human colon can absorb and metabolize RSV depends on the metabolic activity and on the hepatic function of the local intestinal microflora.

Metabolism

RSV undergoes extensive phase I (oxidation, reduction, and hydrolysis) and phase II (glucuronic acid, sulfate, and methyl conjugations) biochemical changes immediately after ingestion (Marier *et al.* 2002), (Yin *et al.* 2016), being metabolized into both glucuronic acid and sulfate conjugations of the phenolic groups in liver and intestinal epithelial cells (Yin *et al.* 2016)(Wenzel *et al.* 2005). Hydrogenation of the aliphatic double bond has also been described [64]. While presystemic and systemic conversion to major metabolites (glucuronic and sulfate conjugations) occur in the intestine and liver very fast and efficiently in the so called enterohepatic recirculation (Marier *et al.* 2002), other metabolites such as dihydro-resveratrol and piceatannol, are probably mediated by microbial fermentation of trans-resveratrol in the gastrointestinal tract. The sulfation of resveratrol in human liver by sulfotransferases (SULTs) has been examined (Varoni *et al.* 2016) and three metabolites were identified: trans-resveratrol-3-O-4'-O-disulfate (S1), transresveratrol- 4'-O-sulfate (S2), and trans-resveratrol-3-O-sulfate (S3). The glucuronidation by uridine 5'-diphospho-glucoronosyltransferases (UGTs) on intestinal absorption of resveratrol was also investigated (Maier-Salamon *et al.* 2006) and it was possible to identify two metabolites, namely, trans-resveratrol-4'-O-glucuronide (G1), and trans-resveratrol-3-O-glucuronide (G2). Modifications such as glucuronidation and sulfation typically reduce the cell permeability to drugs and contribute to their excretionon. However, the in vivo efficacy of the administeredPEG-DOX, despite its low bioavailability, has led some researchers to whether metabolites would be the bioactive forms of the parent compound (Walle *et al.* 2004), (Yin *et al.* 2016). Nevertheless, some studies show less pharmaceutical impact of the metabolites and indicate a decrease in the expression of SULT enzymes in certain types of cancer cells, which indicates an overall low sulfation activity in these cells comparing to the normal ones. Therefore, the reduction of SULT expression may be a favorable factor for achieving better therapeutic effects while an effective dose of trans-RSV is maintained in cancer cell.

Distribution

Blood Transport

The efficiency of a therapeutic substance is often related to its affinity to bind to protein transporters (Khan, Muzammil, et Musarrat 2002). RSV has poor water solubility and thus has to be bound to plasma proteins to ensure its body distribution and bioavailability (Belguendouz, Fremont, et Linard 1997). Jannin *et al.* have(Lu *et al.* 2007)haveinvestigated the binding properties of RSV to plasma proteins, such as human serumalbumin (HSA) and hemoglobin (Hb) and confirmed that both complexes formed arespontaneous and exothermic. The affinity of RSV to HSA complex is higher than that to Hb. Hydrophobic interactions seemto play a major role in the binding of RSV to the hydrophobic cavity of HSA, and hydrogenbonding is the main force involved in the binding of RSV to the central cavity of Hb wheresome residues interact directly with the hydroxyl groups of the compound. Electrostaticinteractions can also be involved in the formation of both complexes since residues withpositive charge are in the proximity of the binding compound (Lu *et al.* 2007).

Liver Uptake

It is known that liver plays a key role in the bioavailability of RSV. Some studies show the highest accumulation of RSV in the liver of rats and mice after oral administration (A. Bertelli *et al.* 1998)(Gambini *et al.* 2015). Nevertheless, no toxicity or hepatocyte lysis was observed after treatment with high doses of RSV, which is relevant because certain antineoplasic agents cause hepatotoxicity, limiting their efficacy in anticancer therapy (Clément *et al.* 1998). Moreover, the large uptake of RSV by liver cells, along with its weak toxicity suggests its important role in the prevention of liver diseases. Besides a passive diffusion influx, it was also shown that RSV enters the liver cells by an active process involving transporters, accounting for more than half of the total hepatic uptake (Jannin *et al.* 2004).

RSV delivery systems

RSV has low bioavailability, and this has been associated with its low stability, its inability to reach a target site and its poor water solubility in the body to exert the desired health effect. Nano-encapsulation allows to improve the solubility of RSV, stabilizing it against trans to cis isomerization, and improving its bioavailability (Stewart *et al.* 1999).

Table 2. RSV effects on hepatic cancer

RSV form (dose)	Model	Study	Output	References
RSV: 20 ans 40 µM.	In vitro:hepatic cell lines (QSG-7701 and LO2) Hepatocellular carcinoma (HCC) CHC-LM3, SMMC-7721 Bel-7402 and HepG 2.	Antitumor efficacy.	The reduction of hexokinase 2,by resveratrol provides a new dimension to clinical HCC therapies aimed at preventing disease progression.	(Dai et al. 2015)
RSV: 10, 20, 50 and 100 µM.	In vitro: HepG2 cells.	Anti-cancer efficacy.	Combination treatment of resveratrol and matrine is a promising novel anticancer strategy for liver cancer; it also provides new insights into the mechanisms of combined therapy.	(Ou et al. 2014)
RVS: 100 mg / kg	In vivo: Mice BALB/c	Hepatotoxicity and neurotoxicity effects.	RSV, rutin, quercetin, and quercetin , would be useful for the clinical treatment of neuro- and hepatoxicity induced by oxaliplatin.	(Schwingel et al. 2014)
RSV: 12.5, 25, 50 and 100 µM.	In vitro: HepG2.	Cytotoxic effects of RSV.	The RSV exerts differential synergistic effect with etoposide on proliferation of cancer cells from different origin which is mainly accompanied by p53 activation.	(Amiri et al. 2013)
RSV: 10, 30, 50, 100, 150 µM.	In vitro: HepG2 cells.	Antiproliferative effects of RSV	RSV added to the culture medium decreased Hepatoma proliferation.	(D. Delmas et al. 2000)
RSV: 100 and 200 µM.	In vitro: AH109A rat ascites hepatoma cells.	Antiproliferative effects of RSV.	RSV inhibited both the proliferation and invasion of AH109A rat ascites hepatoma.	(Kozuki, Miura, et Yagasaki 2001)
RSV: 25, 50, 100 µM.	In vitro: AH109A.	Antiproliferative effects of RSV.	RSV inhibited vascular endothelial growth factor gene expression via hypoxia-inducible factor-1a inhibition.	(Miura, Miura, et Yagasaki 2004)
RSV: 10 µM.	In vitro: HepG2 and Hep3B.	Antiproliferative effects of RSV.	RSV inhibited cell growth only in p53-positive HepG2 cells.	(Kuo, Chiang, et Lin 2002)

A rangeof encapsulation materials, technologies and formulations have been examined for enhancing the delivery of RSV (Stewart *et al.* 1999). Regarding the loadingefficiency, it depends mainly on the lipophilicity of RSV and its affinity to the hydrophobiccore (PCL). The highest drug loading content of RSV into polymeric nanoparticles was about 20% and the encapsulation efficiency was 90% (Shindikar *et al.* 2016), (Shao *et al.* 2009). The cellular uptake of the polymeric nanoparticles occurs by endocytosis, which enhances the drug penetration in cells and. demonstrates higher therapeutic efficiency than the obtained with free drug administration. Solid lipid nanoparticles (SLN) are composed of solid lipids and surfactants and can be used as carriers for RSV because of their size, hydrophobic core with hydrophilic surface, biocompatibility, and also because drug loaded SLN protect drugs from hydrolysis and thus increase drug stability (Müller, Mäder, et Gohla 2000) (Ahlin *et al.* 2000). RSV loaded-SLN were studied regarding the release profile of RSV from SLN and also regarding the cellular uptake of the nanoparticles (Teskac et Kristl 2010).

The controlled release profile of RSV-loaded SLN presents two phases. The first phase corresponds to an initial burst of RSV that is associated with the particle shell. This phase is followed by a prolonged release of the remaining RSV that is located in the lipid matrix (Teskac et Kristl 2010). The efficiency of the SLN cellular uptake depends on the surface properties of these nanocarriers (Matthäus *et al.* 2008). Several molecular interactions are expected when SLN encounters the cell membrane and these interactions may be dependent on several factors such as the biological membrane organization and the existence of lipid rafts (Almeida, Pokorny, et Hinderliter 2005), as well as the formation of actin cytoskeleton invaginations for the receptor mediated entrance (Peetla et Labhasetwar 2008).

SLN may also be considered as a physically stable and well tolerated nanocarrier system. Indeed, with sizes below 180 nm, SLN are able to pass rapidly through membranes causing no significant changes in cell morphology, metabolic activity or cell cycle (Sharma *et al.* 2013). Furthermore, SLN have been reported as excellent delivery systems for RSV being able to carry this bioactive compound until the nuclear target site. Indeed, on the one hand, RSV has multiple actions in cell environment, especially around the nuclear membrane and, on the other hand, SLN intracellular trafficking (Kristl *et al.* 2008). Therefore, it is possible to conclude that SLN can be used as carrier systems to enhance the intracellular delivery of RSV.

Protective effect of antioxidants

General concepts

Polyphenols compounds are widely distributed in the plant kingdom, generally involved in the defense against UV radiation or aggression by pathogens(Manach *et al.* 2005). The most abundant are flavonoids, phenolic acids, lignans, and stilbenes; of these, phenolic acids and flavonoids account for 30% and 60%,respectively of total polyphenols in the diet, approximately 1 g/day (Scalbert, Johnson, et Saltmarsh 2005). The derivatives of the abundant phenolic acids in plants are hydroxycinnamic acids and hydroxybenzoic. (Scalbert, Johnson, et Saltmarsh 2005).

Resveratrol

Resveratrol has been shown to inhibit the hepatic carcinogen-activating enzymes, including cytochrome CYP3A/2 P450 and 1A1 (CYP1A1) and induce hepatic phase 2 conjugating enzymes, namely glutathione S-transferase (GST), UDP-glucuronosyl transferase and NAD (P) H:quinine oxidoreductase, *in vivo and vitro* (Zhu *et al.* 2008), (de la

Lastra et Villegas 2005). The effects of these enzyme modulations by RSV could be the result of reduced exposure of cells to carcinogens due to inhibition of carcinogen activation, elevated carcinogen detoxification and elimination(de la Lastra et Villegas 2005). The of RSV, with regards to liver cancer, is its strong antioxidant properties and anti-inflammatory, as both inflammation and oxidative stress have been strongly implicated in the progression and occurrence of HCC. (Mantovani *et al.* 2008), (Berasain *et al.* 2009), (Kawanishi *et al.* 2006). In vitro and in vivo results showed that RSV make the direct scavenging effect in vitro and may the disclose indirect antioxidant effect by an increase in the expression of intracellular antioxidant enzymes [105]. RSV was prouved to protect hepatic antioxidant systems against ischemia reperfusion-induced oxidative stress, protect from peroxynitrite and oxidative DNA damage caused by hydrogen peroxide (Tomé-Carneiro *et al.* 2013). The oxidative stress and lipid peroxidation are evaluated by MDA level. According to studies realized in vivo, in the RSVtreated rats, levels of MDA were lower than in the AOM group. Glutathione (GSH) plays important role in the protection against oxidative stress, as a cofactor of GSH peroxidases attend in the elimination of hydrogen peroxide and lipid hydroperoxides.

and clinical investigations showed that berberine is beneficial in combating against reactive oxygen species (ROS) formation (Ko *et al.* 2007) (Cho *et al.* 2005). Doxorubicin mainly causes liver injury via the generation of activation of the nuclear factorkappa B and the free radicals. There are not many studies has been carried out concerning the protective effects of berberine on DOX-induced hepatotoxicity. Mice of either gender were randomly divided into four groups: the control group, DOX group, berberine group, and berberine+doxorubicin group. In the tests, body weight, general condition and mortality of the mice were observed, and serum alanine aminotransferase (ALT) and aspartate transaminase (AST) levels were determined to evaluate liver function. DOX caused a series of side effects including decrease of the body weight and liver weight, elevation of serum ALT and AST levels, infiltration of inflammatory cell, and necrosis of hepatocytes. These biochemical and pathological alterations in the mouse model mostly resemble acute liver failure in human. The higher serum aminotransferase activities could be the result of leakage from damaged liver cell membranes after DOX treatment (Pradeep *et al.* 2007). This pretreatment with berberine provided dramatic suppress from damage of mice and ameliorated liver function by lowering serum ALT and AST levels.

Table 3. RSV chemomodulatory effects of RSV to DOX on various cancer cells

RSV,DOX form	Cells	Study	Output	References
DOX: 10 µM, RSV: 100 µM	Colorectal cancer cells HCT 116	Chemomodulatory effects of RES and DID to DOX in colorectal cancer cells.	RSV sensitized colorectal cancer cells to DOX via facilitating apoptosis and enhancing intracellular entrapment of DOX.	(Khaleel et al. 2016)
RSV: 10mg / kg b.wt DOX 5mg / kg b.wt.	In vitro: MCF-7 et MDA-MB-231 In vivo: Albino Mouse	Anti-cancer effects of RSV.	RSV chemosensitizesd DOX in combination, through inhibiting breast cancer cells proliferation and invasion, and inducing apoptosis via suppression of chronic inflammation and autophagy.	(Rai et al. 2016)
DOX: 5 µM RSV: 25 µM	IN vitro: H9c2 cardiac cells	Assess the effects of RSV on sirtuin 1 (SIRT1) activation in mediating DOX-induced cytotoxicity.	RSV protected H9c2 cells against DOX-induced injuries via SIRT1 activation.	(S. Liu et al. 2016)
DOX: 5 µM RSV: 25 µM	In vitro: H9c2	Assess the effects of RSV on AMPK/P53 activation in mediating DOX-induced cytotoxicity.	RSV protected H9c2 cells from DOX-induced apoptosis via the AMPK/P53 pathway.	(Zhao et al. 2016)
RSV: 1-100 µM DOX: 1 µM	In vitro: hematological malignancies K562/ADR	Antiproliferative effects of RSV.	RSV iIncreased anti-proliferative activity of bestatin through downregulating P-Glycoprotein expression via inhibiting PI3K/Akt/mTOR pathway in K562/ADR cells.	(Wang et al. 2016)
RSV: 10/25/50/100 µM	HepG2, Hep3B cells and non-cancerous primary human hepatocytes	Anti-cancer effects of RSV.	Nicotinamide phosphoribosyltransferase (NAMPT) and SIRT1 are differentially regulated by RSVl in hepatocarcinoma cells and primary hepatocytes and that RSV did not act as a SIRT1 activator in hepatocarcinoma cells.	(Schuster et al. 2014)
RSV: 40 µM	In vitro: Hepa1-6 cells	The anticancer effect of curcumin combined with resveratrol in hepatocarcinoma cells.	Combination of curcumin and RSV upregulated intracellular reactive oxygen species (ROS) levels in Hepa1-6 cells.	(Du et al. 2013)
RSV:50, 100, 300 mg / kg	In vivo/ in vivo	Cytotoxic effects of RSV.	RSV-mediated chemoprevention of rat liver carcinogenesis is devoid of any adverse cardiovascular events.	(Luther et al. 2011)

Co-delivery of DOX and antioxidants

DOX and Berberine

Berberine is an alkaloid extracted from coptis, cork and other traditional Chinese medicines that possesses a broad spectrum of pharmacological and therapeutic activités [114], An animal

The histological damages such as inflammatory cell infiltration and necrosis of hepatocytes induced by DOX were also remarkably attenuated by berberine. In agreement with clinical trials on DOX-induced hepatotoxicity, the present data showed that the significant increase in the activities of AST and ALT and histopathological changes in the liver were partially due to DOX therapy. Before and simultaneously treatment of

berberine with DOX protected the liver damage, as indicated from the significant attenuated in body weight and liver weight. Moreover, theelevated ALT and AST levels in the serum were significantly suppressed. The comparative histopathological studies revealed severe destruction of hepaticarchitecture, hemorrhage, necrosis, infiltration of mixed inflammatory cells around the necrotichepatocytes induced by DOX, which are reduced in mice treated with berberine. Administrationwith berberine significantly reduced the liver injury, especially restricted the inflammation andnecrosis to a minor degree. Meanwhile, berberine showed a potency to decrease the increasedhistopathologicalgrade values of the hepatocyte necrosis and inflammatory cell infiltration intoDOX-injured liver. These data suggest that berberine has the potential to protect against toxicity induced by DOX.

Synergstic effects of DPX and RSV

Most recent and significative studies are summarize in table III. Resveratrol sensitized colorectal (Khaleel *et al.* 2016) and breast (Rai *et al.* 2016) cancer cells to DOX via facilitating apoptosis and enhancing intracellular entrapment of DOX and through inhibiting breast cancer cells proliferation and invasion, respectively. DOX-induced either injuries (S. Liu *et al.* 2016) and apoptosis(P. Liu *et al.* 2016). While studying anti-cancer effects of RSV, nicotinamide phosphoribosy ltransferase (NAMPT) and SIRT1 were found to be differentially regulated by RSV in hepatocarcinoma cells and non-cancer primary hepatocytes and RSV did not act as a SIRT1 activator in hepatocarcinoma cells(Schuster *et al.* 2014). Combination of curcumin and RSV upregulated intracellular reactive oxygen species (ROS) levels in Hepa1-6 cells (Du *et al.* 2013).

Conclusion and future directions

Epidemiological data have shown an alarming trend in an increased prevalence of cancer. This tendency, compiled with the disease's high rate of mortality due to limited efficiency of treatment methods. The main therapy and chemotherapy for cancer, but it is a non-specific manner, healthy cells and destroy the tumor cell, has forced researchers to examine preventive approaches as well as alternate routes to treatment. DOX is one of the most frequently used anticancer drugs and the front-line chemotherapeutic options for treating patients with HCC. the clinical applications of DOX are restricted to specific tissue specificity, and especially serious cardio-toxic effects resulted from lipid peroxidation and the generation of free radicals. Over the past decades, nanotechnology has made great contribution to the development of drug delivery systems. Encapsulation of DOX by polymeric nanoparticles (NPs) facilitates drug distribution in tumor tissues through an enhanced permeability and retention (EPR) effect that shows better pharmacokinetics profiles in vivo and reduces multidrug resistance of malignances, leading to enhanced anticancer effects.

Co-delivery of nanoencapsulated DOX plus other drugs within cancer treatment. Using naturally occurring compounds, including those derived from fruits, vegetables and herbs, as potential cancer preventive and therapeutic agents has become a fascinating strategy. RSV stands out as the molecule with the most potential for stifling the disease's consequent mortality rate and growing incidence. From studies using various liver cancer cell lines and chemically-induced tumors as well as

implanted cancers in animal models as described in this review, it becomes apparent that RSV may play an important role not only in the prevention but also in the therapy of metastatic disease of the liver and reduces the toxic effect induced by chemotherapy. All these studies largely establish that RSV has great promise for battling cancer and more exactly the liver cancer. From many studies, have indicated that RSV suppresses the growth of HCC cells and prevents hepato-carcinogenesis by mitigating oxidative stress.

Future research should deal with further characterizing the exact mechanism by which RSV possesses its effects on the cell cycle, apoptosis and redox signaling. However, RSV scavenges modulates activities of antioxidant enzymes and ROS. Future studies should explore these and other possible mechanisms of RSV action to understand the full potential of this dietary agent in the prevention and treatment of HCC. RSV is currently investigated for the prevention and treatment of human colon cancer. It is expected that additional research would lay the foundation for clinical trials with RSV in the prevention of HCC in high-risk patients predisposed with viral hepatitis, other liver diseases and environmental carcinogens.
And RSV has effect against the toxicity induced by chemotherapy, several delivery systems described for RSV such as solution, suspension nanoparticles, nano emulsion RSV and compare it is the form more effective. And see the influences ranging dose of RSV, all this research will be realized on different models: cell cultures, whole animal and isolated organ.

REFERENCES

Aggarwal, Bharat B., Anjana Bhardwaj, Rishi S. Aggarwal, Navindra P. Seeram, Shishir Shishodia, et Yasunari Takada. 2004. « Role of Resveratrol in Prevention and Therapy of Cancer: Preclinical and Clinical Studies ». *Anticancer Research* 24 (5A): 2783⬜2840.

Aggarwal, Bharat B., Shishir Shishodia, Yasunari Takada, Sanjeev Banerjee, Robert A. Newman, Carlos E. Bueso-Ramos, et Janet E. Price. 2005. « Curcumin Suppresses the Paclitaxel-Induced Nuclear Factor-KappaB Pathway in Breast Cancer Cells and Inhibits Lung Metastasis of Human Breast Cancer in Nude Mice ». *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research* 11 (20): 7490⬜98. https://doi.org/10.1158/1078-0432.CCR-05-1192.

Ahlin, P., J. Kristl, M. Sentjurc, J. Strancar, et S. Pecar. 2000. « Influence of Spin Probe Structure on Its Distribution in SLN Dispersions ». *International Journal of Pharmaceutics* 196 (2): 241⬜44.

Ahmadkhani, Lida, Ali Baghban, Shahram Mohammadpoor, Rovshan Khalilov, Abolfazl Akbarzadeh, Taras Kavetskyy, Siamak Saghfi, et Aygun N. Nasibova. 2017. « Synthesis and Evaluation of a Triblock Copolymer/ZnO Nanoparticles from Poly(ε-Caprolactone) and Poly(Acrylic Acid) as a Potential Drug Delivery Carrier ». *Drug Research*, février. https://doi.org/10.1055/s-0042-124190.

Aikemu, Ainiwaer, Nurmuhamat Amat, Abdiryim Yusup, Lianlian Shan, Xinwei Qi, et Halmurat Upur. 2016. « Attenuation Effect of Abnormal Savda Munziq on Liver and Heart Toxicity Caused by Chemotherapy in Mice ». *Experimental and Therapeutic Medicine* 12 (1): 384⬜90. https://doi.org/10.3892/etm.2016.3328.

Allen, T. M. 1998. « Liposomal Drug Formulations. Rationale for Development and What We Can Expect for the Future ». *Drugs* 56 (5): 747□56.

Almeida, Paulo F. F., Antje Pokorny, et Anne Hinderliter. 2005. « Thermodynamics of Membrane Domains ». *Biochimica Et Biophysica Acta* 1720 (1□2): 1□13. https://doi.org/10.1016/j.bbamem.2005.12.004.

Amiri, Fatemehsadat, Amir-Hassan Zarnani, Hamid Zand, Fariba Koohdani, Mahmood Jeddi-Tehrani, et Mohammadreza Vafa. 2013. « Synergistic Anti-Proliferative Effect of Resveratrol and Etoposide on Human Hepatocellular and Colon Cancer Cell Lines ». *European Journal of Pharmacology* 718 (1□3): 34□40. https://doi.org/10.1016/j.ejphar.2013.09.020.

Baur, Joseph A., et David A. Sinclair. 2006. « Therapeutic Potential of Resveratrol: The in Vivo Evidence ». *Nature Reviews. Drug Discovery* 5 (6): 493□506. https://doi.org/10.1038/nrd2060.

Belguendouz, L., L. Fremont, et A. Linard. 1997. « Resveratrol Inhibits Metal Ion-Dependent and Independent Peroxidation of Porcine Low-Density Lipoproteins ». *Biochemical Pharmacology* 53 (9): 1347□55.

Berasain, C., J. Castillo, M. J. Perugorria, M. U. Latasa, J. Prieto, et M. A. Avila. 2009. « Inflammation and Liver Cancer: New Molecular Links ». *Annals of the New York Academy of Sciences* 1155 (février): 206□21. https://doi.org/10.1111/j.1749-6632.2009.03704.x.

Bertelli, A. A., L. Giovannini, R. Stradi, S. Urien, J. P. Tillement, et A. Bertelli. 1996. « Kinetics of Trans- and Cis-Resveratrol (3,4',5-Trihydroxystilbene) after Red Wine Oral Administration in Rats ». *International Journal of Clinical Pharmacology Research* 16 (4□5): 77□81.

Bertelli, A., A. A. Bertelli, A. Gozzini, et L. Giovannini. 1998. « Plasma and Tissue Resveratrol Concentrations and Pharmacological Activity ». *Drugs Under Experimental and Clinical Research* 24 (3): 133□38.

Buzdar, A. U., C. Marcus, T. L. Smith, et G. R. Blumenschein. 1985. « Early and Delayed Clinical Cardiotoxicity of Doxorubicin ». *Cancer* 55 (12): 2761□65.

Cho, Bong-Jun, Eun Kyoung Im, Jun Hye Kwon, Kyung-Hye Lee, Hye-Jin Shin, Jaewon Oh, Seok-Min Kang, Ji Hyung Chung, et Yangsoo Jang. 2005. « Berberine Inhibits the Production of Lysophosphatidylcholine-Induced Reactive Oxygen Species and the ERK1/2 Pathway in Vascular Smooth Muscle Cells ». *Molecules and Cells* 20 (3): 429□34.

Clément, M. V., J. L. Hirpara, S. H. Chawdhury, et S. Pervaiz. 1998. « Chemopreventive Agent Resveratrol, a Natural Product Derived from Grapes, Triggers CD95 Signaling-Dependent Apoptosis in Human Tumor Cells ». *Blood* 92 (3): 996□1002.

Cowens, J. W., P. J. Creaven, W. R. Greco, D. E. Brenner, Y. Tung, M. Ostro, F. Pilkiewicz, R. Ginsberg, et N. Petrelli. 1993. « Initial Clinical (Phase I) Trial of TLC D-99 (Doxorubicin Encapsulated in Liposomes) ». *Cancer Research* 53 (12): 2796□2802.

Dai, Weiqi, Fan Wang, Jie Lu, Yujing Xia, Lei He, Kan Chen, Jingjing Li, et al. 2015. « By Reducing Hexokinase 2, Resveratrol Induces Apoptosis in HCC Cells Addicted to Aerobic Glycolysis and Inhibits Tumor Growth in Mice ». *Oncotarget* 6 (15): 13703. https://doi.org/10.18632/oncotarget.3800.

Das, Surajit, et Ka-Yun Ng. 2011. « Quantification of Trans-Resveratrol in Rat Plasma by a Simple and Sensitive High Performance Liquid Chromatography Method and Its Application in Pre-Clinical Study ». *Journal of Liquid Chromatography & Related Technologies* 34 (14): 1399□1414. https://doi.org/10.1080/10826076.2011.572215.

Delmas, D., B. Jannin, M. Cherkaoui Malki, et N. Latruffe. 2000. « Inhibitory Effect of Resveratrol on the Proliferation of Human and Rat Hepatic Derived Cell Lines ». *Oncology Reports* 7 (4): 847□52.

Delmas, Dominique, Allan Lançon, Didier Colin, Brigitte Jannin, et Norbert Latruffe. 2006. « Resveratrol as a Chemopreventive Agent: A Promising Molecule for Fighting Cancer ». *Current Drug Targets* 7 (4): 423□42.

Di Lorenzo, Giuseppe, Antonio Rea, Chiara Carlomagno, Stefano Pepe, Giovannella Palmieri, Roberto Labianca, Antonio Chirianni, et al. 2007. « Activity and Safety of Pegylated Liposomal Doxorubicin, 5-Fluorouracil and Folinic Acid in Inoperable Hepatocellular Carcinoma: A Phase II Study ». *World Journal of Gastroenterology* 13 (48): 6553□57.

Doroshow, J. H. 1983. « Anthracycline Antibiotic-Stimulated Superoxide, Hydrogen Peroxide, and Hydroxyl Radical Production by NADH Dehydrogenase ». *Cancer Research* 43 (10): 4543□51.

Du, Qin, Bing Hu, Hong-Mei An, Ke-Ping Shen, Ling Xu, Shan Deng, et Meng-Meng Wei. 2013. « Synergistic Anticancer Effects of Curcumin and Resveratrol in Hepa1-6 Hepatocellular Carcinoma Cells ». *Oncology Reports* 29 (5): 1851□58. https://doi.org/10.3892/or.2013.2310.

Gambini, J., M. Inglés, G. Olaso, R. Lopez-Grueso, V. Bonet-Costa, L. Gimeno-Mallench, C. Mas-Bargues, et al. 2015. « Properties of Resveratrol: In Vitro and In Vivo Studies about Metabolism, Bioavailability, and Biological Effects in Animal Models and Humans ». *Oxidative Medicine and Cellular Longevity* 2015: 837042. https://doi.org/10.1155/2015/837042.

Ghorbani, Marjan, et Hamed Hamishehkar. 2017. « Redox and PH-Responsive Gold Nanoparticles as a New Platform for Simultaneous Triple Anti-Cancer Drugs Targeting ». *International Journal of Pharmaceutics* 520 (1□2): 126□38. https://doi.org/10.1016/j.ijpharm.2017.02.008.

Goldberg, David M., Joseph Yan, et George J. Soleas. 2003. « Absorption of Three Wine-Related Polyphenols in Three Different Matrices by Healthy Subjects ». *Clinical Biochemistry* 36 (1): 79□87.

Goswami, Shyamal K., et Dipak K. Das. 2009. « Resveratrol and Chemoprevention ». *Cancer Letters* 284 (1): 1□6. https://doi.org/10.1016/j.canlet.2009.01.041.

Hamlaoui, S., M. Mokni, N. Limam, A. Carrier, F. Limam, M. Amri, L. Marzouki, et E. Aouani. 2012. « Resveratrol Protects against Acute Chemotherapy Toxicity Induced by Doxorubicin on Rat Erythrocyte and Plasma ». *Journal of Physiology and Pharmacology: An Official Journal of the Polish Physiological Society* 63 (3): 293□301.

Haran, G., R. Cohen, L. K. Bar, et Y. Barenholz. 1993. « Transmembrane Ammonium Sulfate Gradients in Liposomes Produce Efficient and Stable Entrapment of Amphipathic Weak Bases ». *Biochimica Et Biophysica Acta* 1151 (2): 201□15.

Hodnick, W. F., F. S. Kung, W. J. Roettger, C. W. Bohmont, et R. S. Pardini. 1986. « Inhibition of Mitochondrial Respiration and Production of Toxic Oxygen Radicals by Flavonoids. A Structure-Activity Study ». *Biochemical Pharmacology* 35 (14): 2345□57.

Jannin, Brigitte, Matthias Menzel, Jean-Pierre Berlot, Dominique Delmas, Allan Lançon, et Norbert Latruffe.

2004. « Transport of Resveratrol, a Cancer Chemopreventive Agent, to Cellular Targets: Plasmatic Protein Binding and Cell Uptake ». *Biochemical Pharmacology* 68 (6): 1113□18. https://doi.org/10.1016/j.bcp.2004.04.028.

Kalender, Suna, Yusuf Kalender, Ayşe Ogutcu, Meltem Uzunhisarcikli, Dilek Durak, et Fatma Açikgoz. 2004. « Endosulfan-Induced Cardiotoxicity and Free Radical Metabolism in Rats: The Protective Effect of Vitamin E ». *Toxicology* 202 (3): 227□35. https://doi.org/10.1016/j.tox.2004.05.010.

Kalender, Yusuf, Mustafa Yel, et Suna Kalender. 2005. « Doxorubicin hepatotoxicity and hepatic free radical metabolism in rats: The effects of vitamin E and catechin ». *Toxicology* 209 (1): 39□45. https://doi.org/10.1016/j.tox.2004.12.003.

Kassner, Nina, Klaus Huse, Hans-Jörg Martin, Ute Gödtel-Armbrust, Annegret Metzger, Ingolf Meineke, Jürgen Brockmöller, et al. 2008. « Carbonyl Reductase 1 Is a Predominant Doxorubicin Reductase in the Human Liver ». *Drug Metabolism and Disposition: The Biological Fate of Chemicals* 36 (10): 2113□20. https://doi.org/10.1124/dmd.108.022251.

Kawanishi, Shosuke, Yusuke Hiraku, Somchai Pinlaor, et Ning Ma. 2006. « Oxidative and Nitrative DNA Damage in Animals and Patients with Inflammatory Diseases in Relation to Inflammation-Related Carcinogenesis ». *Biological Chemistry* 387 (4): 365□72. https://doi.org/10.1515/BC.2006.049.

Khaleel, Sahar A., Ahmed M. Al-Abd, Azza A. Ali, et Ashraf B. Abdel-Naim. 2016. « Didox and Resveratrol Sensitize Colorectal Cancer Cells to Doxorubicin via Activating Apoptosis and Ameliorating P-Glycoprotein Activity ». *Scientific Reports* 6 (novembre): 36855. https://doi.org/10.1038/srep36855.

Khan, Mateen A., Salman Muzammil, et Javed Musarrat. 2002. « Differential Binding of Tetracyclines with Serum Albumin and Induced Structural Alterations in Drug-Bound Protein ». *International Journal of Biological Macromolecules* 30 (5): 243□49.

Kim, Hyo Jin, Eun Ju Chang, Song Ja Bae, Sun Mi Shim, Heui Dong Park, Chang Ho Rhee, Jun Hong Park, et Sang Won Choi. 2002. « Cytotoxic and Antimutagenic Stilbenes from Seeds of Paeonia Lactiflora ». *Archives of Pharmacal Research* 25 (3): 293□99.

Ko, Yu Jin, Jong-Suk Lee, Byung Chul Park, Heung Mook Shin, et Jung-Ae Kim. 2007. « Inhibitory Effects of Zoagumhwan Water Extract and Berberine on Angiotensin II-Induced Monocyte Chemoattractant Protein (MCP)-1 Expression and Monocyte Adhesion to Endothelial Cells ». *Vascular Pharmacology* 47 (2□3): 189□96. https://doi.org/10.1016/j.vph.2007.06.004.

Kocsis, Zsuzsanna, Zoltán L. Marcsek, Mátyás G. Jakab, Béla Szende, et Anna Tompa. 2005. « Chemopreventive Properties of Trans-Resveratrol against the Cytotoxicity of Chloroacetanilide Herbicides in Vitro ». *International Journal of Hygiene and Environmental Health* 208 (3): 211□18. https://doi.org/10.1016/j.ijheh.2005.01.021.

Kozluca, O., E. Olcay, S. Sürücü, Z. Güran, T. Kulaksiz, et N. Uskent. 1996. « Prevention of Doxorubicin Induced Cardiotoxicity by Catechin ». *Cancer Letters* 99 (1): 1□6.

Kozuki, Y., Y. Miura, et K. Yagasaki. 2001. « Resveratrol Suppresses Hepatoma Cell Invasion Independently of Its Anti-Proliferative Action ». *Cancer Letters* 167 (2): 151□56.

Kristl, Julijana, Karmen Teskac, Miha Milek, et Irena Mlinaric-Rascan. 2008. « Surface Active Stabilizer Tyloxapol in Colloidal Dispersions Exerts Cytostatic Effects and Apoptotic Dismissal of Cells ». *Toxicology and Applied Pharmacology* 232 (2): 218□25. https://doi.org/10.1016/j.taap.2008.06.019.

Kuo, Po-Lin, Lien-Chai Chiang, et Chun-Ching Lin. 2002. « Resveratrol- Induced Apoptosis Is Mediated by P53-Dependent Pathway in Hep G2 Cells ». *Life Sciences* 72 (1): 23□34.

Lasic, D. D., F. J. Martin, A. Gabizon, S. K. Huang, et D. Papahadjopoulos. 1991. « Sterically Stabilized Liposomes: A Hypothesis on the Molecular Origin of the Extended Circulation Times ». *Biochimica Et Biophysica Acta* 1070 (1): 187□92.

Lastra, Catalina Alarcón de la, et Isabel Villegas. 2005. « Resveratrol as an Anti-Inflammatory and Anti-Aging Agent: Mechanisms and Clinical Implications ». *Molecular Nutrition & Food Research* 49 (5): 405□30. https://doi.org/10.1002/mnfr.200500022.

Lefrak, E. A., J. Pitha, S. Rosenheim, et J. A. Gottlieb. 1973. « A Clinicopathologic Analysis of Adriamycin Cardiotoxicity ». *Cancer* 32 (2): 302□14.

Lin, Bin, Hui Yu, Yongzhi He, Yang Xu, Wenbin Zhang, Chengwu Lu, et Qingfang Ao. 2016. « Protective Effects of Resveratrol on Autologous Nucleus Pulposus Model of Radiculopathy ». *Experimental and Therapeutic Medicine* 12 (6): 3917□22. https://doi.org/10.3892/etm.2016.3878.

Liu, Peng, Yongluan Lin, Xiuying Tang, Peidong Zhang, Bei Liu, Yingfeng Liu, et Fei Miao. 2016. « Helix B Surface Peptide Protects Cardiomyocytes Against Hypoxia/Reoxygenation-Induced Apoptosis Through Mitochondrial Pathways ». *Journal of Cardiovascular Pharmacology* 67 (5): 418□26. https://doi.org/10.1097/FJC.0000000000000367.

Liu, Shan, Wei Wei, Bo Xie, Hua Yue, Dezhi Ni, Yali Bao, Guanghui Ma, et Zhiguo G. Su. 2016. « Breaching the Hyaluronan Barrier with PH20-Fc Facilitates Intratumoral Permeation and Enhances Antitumor Efficiency: A Comparative Investigation of Typical Therapeutic Agents in Different Nanoscales ». *Advanced Healthcare Materials* 5 (22): 2872□81. https://doi.org/10.1002/adhm.201600528.

Liu, Zehua, Vimalkumar Balasubramanian, Chinmay Bhat, Mikko Vahermo, Ermei Mäkilä, Marianna Kemell, Flavia Fontana, et al. 2017. « Quercetin-Based Modified Porous Silicon Nanoparticles for Enhanced Inhibition of Doxorubicin-Resistant Cancer Cells ». *Advanced Healthcare Materials* 6 (3). https://doi.org/10.1002/adhm.201601009.

Lu, Zhong, Yuying Zhang, Hui Liu, Jianglan Yuan, Zhongliang Zheng, et Guolin Zou. 2007. « Transport of a Cancer Chemopreventive Polyphenol, Resveratrol: Interaction with Serum Albumin and Hemoglobin ». *Journal of Fluorescence* 17 (5): 580□87. https://doi.org/10.1007/s10895-007-0220-2.

Luther, Daniel J., Vahagn Ohanyan, Patricia E. Shamhart, Cheryl M. Hodnichak, Hamayak Sisakian, Tristan D. Booth, J. Gary Meszaros, et Anupam Bishayee. 2011. « Chemopreventive Doses of Resveratrol Do Not Produce Cardiotoxicity in a Rodent Model of Hepatocellular Carcinoma ». *Investigational New Drugs* 29 (2): 380□91. https://doi.org/10.1007/s10637-009-9332-7.

Maier-Salamon, Alexandra, Birgit Hagenauer, Michael Wirth, Franz Gabor, Thomas Szekeres, et Walter Jäger. 2006. « Increased Transport of Resveratrol across Monolayers of

the Human Intestinal Caco-2 Cells Is Mediated by Inhibition and Saturation of Metabolites ». *Pharmaceutical Research* 23 (9): 2107□15. https://doi.org/10.1007/s11095-006-9060-z.

Manach, Claudine, Gary Williamson, Christine Morand, Augustin Scalbert, et Christian Rémésy. 2005. « Bioavailability and Bioefficacy of Polyphenols in Humans. I. Review of 97 Bioavailability Studies ». *The American Journal of Clinical Nutrition* 81 (1 Suppl): 230S-242S.

Mantovani, Alberto, Paola Allavena, Antonio Sica, et Frances Balkwill. 2008. « Cancer-Related Inflammation ». *Nature* 454 (7203): 436□44. https://doi.org/10.1038/nature07205.

Marchand, D. J., et K. W. Renton. 1981. « Depression of Cytochrome P-450-Dependent Drug Biotransformation by Adriamycin ». *Toxicology and Applied Pharmacology* 58 (1): 83□88.

Margarida Cardoso, M., Inês N. Peça, Cláudia D. Raposo, Krasimira T. Petrova, M. Teresa Barros, Rui Gardner, et A. Bicho. 2016. « Doxorubicin-Loaded Galactose-Conjugated Poly(d,l-Lactide-Co-Glycolide) Nanoparticles as Hepatocyte-Targeting Drug Carrier ». *Journal of Microencapsulation* 33 (4): 315□22. https://doi.org/10.1080/02652048.2016.1185474.

Marier, Jean-Francois, Pascal Vachon, Ari Gritsas, Jie Zhang, Jean-Pierre Moreau, et Murray P. Ducharme. 2002. « Metabolism and Disposition of Resveratrol in Rats: Extent of Absorption, Glucuronidation, and Enterohepatic Recirculation Evidenced by a Linked-Rat Model ». *The Journal of Pharmacology and Experimental Therapeutics* 302 (1): 369□73.

Matsumura, Y., T. Hamaguchi, T. Ura, K. Muro, Y. Yamada, Y. Shimada, K. Shirao, et al. 2004. « Phase I Clinical Trial and Pharmacokinetic Evaluation of NK911, a Micelle-Encapsulated Doxorubicin ». *British Journal of Cancer* 91 (10): 1775. https://doi.org/10.1038/sj.bjc.6602204.

Matthäus, Christian, Amit Kale, Tatyana Chernenko, Vladimir Torchilin, et Max Diem. 2008. « New Ways of Imaging Uptake and Intracellular Fate of Liposomal Drug Carrier Systems inside Individual Cells, Based on Raman Microscopy ». *Molecular Pharmaceutics* 5 (2): 287□93. https://doi.org/10.1021/mp7001158.

Mitra, S., U. Gaur, P. C. Ghosh, et A. N. Maitra. 2001. « Tumour Targeted Delivery of Encapsulated Dextran-Doxorubicin Conjugate Using Chitosan Nanoparticles as Carrier ». *Journal of Controlled Release: Official Journal of the Controlled Release Society* 74 (1□3): 317□23.

Miura, Daiki, Yutaka Miura, et Kazumi Yagasaki. 2004. « Resveratrol Inhibits Hepatoma Cell Invasion by Suppressing Gene Expression of Hepatocyte Growth Factor via Its Reactive Oxygen Species-Scavenging Property ». *Clinical & Experimental Metastasis* 21 (5): 445□51.

Montgomery, Megan D., Trevor Chan, Philip M. Swigart, Bat-Erdene Myagmar, Rajesh Dash, et Paul C. Simpson. 2017. « An Alpha-1A Adrenergic Receptor Agonist Prevents Acute Doxorubicin Cardiomyopathy in Male Mice ». *PloS One* 12 (1): e0168409. https://doi.org/10.1371/journal.pone.0168409.

Müller, R. H., K. Mäder, et S. Gohla. 2000. « Solid Lipid Nanoparticles (SLN) for Controlled Drug Delivery - a Review of the State of the Art ». *European Journal of Pharmaceutics and Biopharmaceutics: Official Journal of Arbeitsgemeinschaft Fur Pharmazeutische Verfahrenstechnik e.V* 50 (1): 161□77.

Nagai, Katsuhito, Shuhei Fukuno, Ayano Oda, et Hiroki Konishi. 2016. « Protective Effects of Taurine on Doxorubicin-Induced Acute Hepatotoxicity through Suppression of Oxidative Stress and Apoptotic Responses ». *Anti-Cancer Drugs* 27 (1): 17□23. https://doi.org/10.1097/CAD.0000000000000299.

Niles, Richard M., Carla P. Cook, Gary G. Meadows, Ya-Min Fu, Jerry L. McLaughlin, et Gary O. Rankin. 2006. « Resveratrol Is Rapidly Metabolized in Athymic (Nu/Nu) Mice and Does Not Inhibit Human Melanoma Xenograft Tumor Growth ». *The Journal of Nutrition* 136 (10): 2542□46.

Ou, Xiuyuan, Yan Chen, Xinxin Cheng, Xumeng Zhang, et Qiyang He. 2014. « Potentiation of resveratrol-induced apoptosis by matrine in human hepatoma HepG2 cells ». *Oncology Reports* 32 (6): 2803□9.

Peetla, Chiranjeevi, et Vinod Labhasetwar. 2008. « Biophysical Characterization of Nanoparticle-Endothelial Model Cell Membrane Interactions ». *Molecular Pharmaceutics* 5 (3): 418□29. https://doi.org/10.1021/mp700140a.

Pereira-Caro, Gema, Beatriz Sarriá, Andrés Madrona, José Luis Espartero, Luis Goya, Laura Bravo, et Raquel Mateos. 2011. « Alkyl Hydroxytyrosyl Ethers Show Protective Effects against Oxidative Stress in HepG2 Cells ». *Journal of Agricultural and Food Chemistry* 59 (11): 5964□76. https://doi.org/10.1021/jf2002415.

Pradeep, Kannampalli, Chandrasekaran Victor Raj Mohan, Kuppannan Gobianand, et Sivanesan Karthikeyan. 2007. « Effect of Cassia Fistula Linn. Leaf Extract on Diethylnitrosamine Induced Hepatic Injury in Rats ». *Chemico-Biological Interactions* 167 (1): 12□18. https://doi.org/10.1016/j.cbi.2006.12.011.

Pranatharthiharan, Sandhya, Mitesh D. Patel, Vinod C. Malshe, Vaishali Pujari, Ajit Gorakshakar, Manisha Madkaikar, Kanjaksha Ghosh, et Padma V. Devarajan. 2017. « Asialoglycoprotein Receptor Targeted Delivery of Doxorubicin Nanoparticles for Hepatocellular Carcinoma ». *Drug Delivery* 24 (1): 20□29. https://doi.org/10.1080/10717544.2016.1225856.

Quiles, José L., Jesús R. Huertas, Maurizio Battino, José Mataix, et M. Carmen Ramírez-Tortosa. 2002. « Antioxidant Nutrients and Adriamycin Toxicity ». *Toxicology* 180 (1): 79□95.

Rai, Girish, Sanjay Mishra, Shankar Suman, et Yogeshwer Shukla. 2016. « Resveratrol Improves the Anticancer Effects of Doxorubicin in Vitro and in Vivo Models: A Mechanistic Insight ». *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology* 23 (3): 233□42. https://doi.org/10.1016/j.phymed.2015.12.020.

Scalbert, Augustin, Ian T. Johnson, et Mike Saltmarsh. 2005. « Polyphenols: Antioxidants and Beyond ». *The American Journal of Clinical Nutrition* 81 (1 Suppl): 215S-217S.

Schuster, Susanne, Melanie Penke, Theresa Gorski, Stefanie Petzold-Quinque, Georg Damm, Rolf Gebhardt, Wieland Kiess, et Antje Garten. 2014. « Resveratrol Differentially Regulates NAMPT and SIRT1 in Hepatocarcinoma Cells and Primary Human Hepatocytes ». *PloS One* 9 (3): e91045. https://doi.org/10.1371/journal.pone.0091045.

Schwingel, Tania E., Caroline P. Klein, Natalia F. Nicoletti, Cristiana L. Dora, Gabriela Hadrich, Cláudia G. Bica, Tiago G. Lopes, Vinicius Duval da Silva, et Fernanda B. Morrone. 2014. « Effects of the Compounds Resveratrol, Rutin, Quercetin, and Quercetin Nanoemulsion on Oxaliplatin-Induced Hepatotoxicity and Neurotoxicity in

Mice ». *Naunyn-Schmiedeberg's Archives of Pharmacology* 387 (9): 837□48. https://doi.org/10.1007/s00210-014-0994-0.

Shakibaei, Mehdi, Kuzhuvelil B. Harikumar, et Bharat B. Aggarwal. 2009. « Resveratrol Addiction: To Die or Not to Die ». *Molecular Nutrition & Food Research* 53 (1): 115□28. https://doi.org/10.1002/mnfr.200800148.

Shao, Junfei, Xiaolin Li, Xiaowei Lu, Chen Jiang, Yong Hu, Qingping Li, Yongping You, et Zhen Fu. 2009. « Enhanced Growth Inhibition Effect of Resveratrol Incorporated into Biodegradable Nanoparticles against Glioma Cells Is Mediated by the Induction of Intracellular Reactive Oxygen Species Levels ». *Colloids and Surfaces. B, Biointerfaces* 72 (1): 40□47. https://doi.org/10.1016/j.colsurfb.2009.03.010.

Sharma, Blanka, Chiranjeevi Peetla, Isaac M. Adjei, et Vinod Labhasetwar. 2013. « Selective Biophysical Interactions of Surface Modified Nanoparticles with Cancer Cell Lipids Improve Tumor Targeting and Gene Therapy ». *Cancer Letters* 334 (2): 228□36. https://doi.org/10.1016/j.canlet.2013.03.011.

Shindikar, Amol, Akshita Singh, Malcolm Nobre, et Saurabh Kirolikar. 2016. « Curcumin and Resveratrol as Promising Natural Remedies with Nanomedicine Approach for the Effective Treatment of Triple Negative Breast Cancer ». *Journal of Oncology* 2016: 9750785. https://doi.org/10.1155/2016/9750785.

Stervbo, U., O. Vang, et C. Bonnesen. 2006. « Time- and Concentration-Dependent Effects of Resveratrol in HL-60 and HepG2 Cells ». *Cell Proliferation* 39 (6): 479□93. https://doi.org/10.1111/j.1365-2184.2006.00406.x.

Stewart, J. R., N. E. Ward, C. G. Ioannides, et C. A. O'Brian. 1999. « Resveratrol Preferentially Inhibits Protein Kinase C-Catalyzed Phosphorylation of a Cofactor-Independent, Arginine-Rich Protein Substrate by a Novel Mechanism ». *Biochemistry* 38 (40): 13244□51.

Tacar, Oktay, Pornsak Sriamornsak, et Crispin R. Dass. 2013. « Doxorubicin: An Update on Anticancer Molecular Action, Toxicity and Novel Drug Delivery Systems ». *The Journal of Pharmacy and Pharmacology* 65 (2): 157□70. https://doi.org/10.1111/j.2042-7158.2012.01567.x.

Tan, Mei L., Anna M. Friedhuber, Dave E. Dunstan, Peter F. M. Choong, et Crispin R. Dass. 2010. « The Performance of Doxorubicin Encapsulated in Chitosan-Dextran Sulphate Microparticles in an Osteosarcoma Model ». *Biomaterials* 31 (3): 541□51. https://doi.org/10.1016/j.biomaterials.2009.09.069.

Teskac, K., et J. Kristl. 2010. « The Evidence for Solid Lipid Nanoparticles Mediated Cell Uptake of Resveratrol ». *International Journal of Pharmaceutics* 390 (1): 61□69. https://doi.org/10.1016/j.ijpharm.2009.10.011.

Tomé-Carneiro, Joao, Mar Larrosa, Antonio González-Sarrías, Francisco A. Tomás-Barberán, María Teresa García-Conesa, et Juan Carlos Espín. 2013. « Resveratrol and Clinical Trials: The Crossroad from In Vitro Studies to Human Evidence ». *Current Pharmaceutical Design* 19 (34): 6064. https://doi.org/10.2174/13816128113199990407.

Udhrain, Ashish, Keith M. Skubitz, et Donald W. Northfelt. 2007. « Pegylated Liposomal Doxorubicin in the Treatment of AIDS-Related Kaposi's Sarcoma ». *International Journal of Nanomedicine* 2 (3): 345.

Varoni, Elena M., Alfredo Fabrizio Lo Faro, Javad Sharifi-Rad, et Marcello Iriti. 2016. « Anticancer Molecular

Mechanisms of Resveratrol ». *Frontiers in Nutrition* 3: 8. https://doi.org/10.3389/fnut.2016.00008.

Walle, Thomas, Faye Hsieh, Mark H. DeLegge, John E. Oatis, et U. Kristina Walle. 2004. « High Absorption but Very Low Bioavailability of Oral Resveratrol in Humans ». *Drug Metabolism and Disposition: The Biological Fate of Chemicals* 32 (12): 1377□82. https://doi.org/10.1124/dmd.104.000885.

Wang, Li, Changyuan Wang, Yongming Jia, Zhihao Liu, Xiaohong Shu, et Kexin Liu. 2016. « Resveratrol Increases Anti-Proliferative Activity of Bestatin Through Downregulating P-Glycoprotein Expression Via Inhibiting PI3K/Akt/MTOR Pathway in K562/ADR Cells ». *Journal of Cellular Biochemistry* 117 (5): 1233□39. https://doi.org/10.1002/jcb.25407.

Wenzel, Elisabeth, Tomislav Soldo, Helmut Erbersdobler, et Veronika Somoza. 2005. « Bioactivity and Metabolism of Trans-Resveratrol Orally Administered to Wistar Rats ». *Molecular Nutrition & Food Research* 49 (5): 482□94. https://doi.org/10.1002/mnfr.200500003.

Working, Peter K., Mary S. Newman, Timothy Sullivan, et John Yarrington. 1999. « Reduction of the Cardiotoxicity of Doxorubicin in Rabbits and Dogs by Encapsulation in Long-Circulating, Pegylated Liposomes ». *Journal of Pharmacology and Experimental Therapeutics* 289 (2): 1128□33.

Xiong, Hejian, Dongfang Zhou, Yanxin Qi, Zhiyun Zhang, Zhigang Xie, Xuesi Chen, Xiabin Jing, Fanbo Meng, et Yubin Huang. 2015. « Doxorubicin-Loaded Carborane-Conjugated Polymeric Nanoparticles as Delivery System for Combination Cancer Therapy ». *Biomacromolecules* 16 (12): 3980□88. https://doi.org/10.1021/acs.biomac.5b01311.

Yin, Teng-Fei, Min Wang, Ying Qing, Ying-Min Lin, et Dong Wu. 2016. « Research Progress on Chemopreventive Effects of Phytochemicals on Colorectal Cancer and Their Mechanisms ». *World Journal of Gastroenterology* 22 (31): 7058□68. https://doi.org/10.3748/wjg.v22.i31.7058.

Zhang, Qunzhou, Xudong Tang, Qing Yi Lu, Zuo Feng Zhang, Jimmy Brown, et Anh D. Le. 2005. « Resveratrol Inhibits Hypoxia-Induced Accumulation of Hypoxia-Inducible Factor-1alpha and VEGF Expression in Human Tongue Squamous Cell Carcinoma and Hepatoma Cells ». *Molecular Cancer Therapeutics* 4 (10): 1465□74. https://doi.org/10.1158/1535-7163.MCT-05-0198.

Zhang, Shuang, Hong Li, Hui Xu, et Shi-Jie Yang. 2010. « [Effect of gross saponins of Tribulus terrestris on cardiocytes impaired by adriamycin] ». *Yao Xue Xue Bao = Acta Pharmaceutica Sinica* 45 (1): 31□36.

Zhao, Wenjun, Aiyun Li, Xin Feng, Ting Hou, Kang Liu, Baolin Liu, et Ning Zhang. 2016. « Data on Biochemical Indexes of HFD-Fed Mice Treatment with Metformin or Resveratrol ». *Data in Brief* 8 (septembre): 1190□93. https://doi.org/10.1016/j.dib.2016.07.049.

Zheng, Zongyu, Paul Pavlidis, Streamson Chua, Vivette D. D'Agati, et Ali G. Gharavi. 2006. « An Ancestral Haplotype Defines Susceptibility to Doxorubicin Nephropathy in the Laboratory Mouse ». *Journal of the American Society of Nephrology: JASN* 17 (7): 1796□1800. https://doi.org/10.1681/ASN.2005121373.

Zhou, Xuelin, Ching Mei Cheung, Jia-Ming Yang, Penelope M. Y. Or, Wayne Y. W. Lee, et John H. K. Yeung. 2015. « Danshen (Salvia Miltiorrhiza) Water Extract Inhibits Paracetamol-Induced Toxicity in Primary Rat Hepatocytes via Reducing CYP2E1 Activity and Oxidative Stress ». *The*

Journal of Pharmacy and Pharmacology 67 (7): 980□89. https://doi.org/10.1111/jphp.12381.

Zhu, Jian, Wei Yong, Xiaohong Wu, Ying Yu, Jinghuan Lv, Cuiping Liu, Xiaodong Mao, et al. 2008. « Anti-
Inflammatory Effect of Resveratrol on TNF-Alpha-Induced MCP-1 Expression in Adipocytes ». *Biochemical and Biophysical Research Communications* 369 (2): 471□77. https://doi.org/10.1016/j.bbrc.2008.02.034.

****