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Multifaceted approach to resveratrol bioactivity

Focus on antioxidant action, cell signaling and safety

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Abbreviations: RVT, resveratrol; ET, electron transfer; ROS, reactive oxygen species; OS, oxidative stress; AO, antioxidant; CNS, central nervous system; ATP, adenosine triphosphate; GSH, glutathione; NO, nitric oxide; 8-OH-dG, 8-hydroxy-d-guanosine; PCB, polychlorinated biphenyl; AR, androgen receptor; SOD, superoxide dismutase; AA, amino acid

Resveratrol (RVT) is a naturally occurring trihydroxy stilbene that displays a wide spectrum of physiological activity. Its ability to behave therapeutically as a component of red wine has attracted wide attention. The phenol acts as a protective agent involving various body constituents. Most attention has been given to beneficial effects in insults involving cancer, aging, cardiovascular system, inflammation and the central nervous system. One of the principal modes of action appears to be as antioxidant. Other mechanistic pathways entail cell signaling, apoptosis and gene expression. There is an intriguing dichotomy in relation to pro-oxidant property. Also discussed are metabolism, receptor binding, rationale for safety and suggestions for future work. This is the first comprehensive review of RVT based on a broad, unifying mechanism.

Introduction

Resveratrol 1 (**Fig. 1**) (RVT) is a naturally occurring stilbene derivative that possesses three phenolic groups, two of which are part of a resorcinol structure. Most work involves the naturally occurring trans isomer. It is present in various dietary sources, including grapes, peanuts, plums and many plants. Much recent attention was paid to the "French paradox" (see below) which provides evidence for the beneficial effects of red wine. Investigations pointed to RVT as the principal therapeutic agent. The literature contains voluminous reports on the wide variety of properties by the phenol. Most attention has been devoted to anticancer, anti-aging, anti-inflammatory, cardioprotection and countering of insults to the central nervous system. Articles document a large number of mechanisms involved in the biological activity. One of the most important is the antioxidant (AO) attribute. Considerable literature correlates the presence of reactive oxygen species (ROS) to oxidative stress (OS) leading to large numbers of adverse effects suffered by body constituents. Hence, it is reasonable to assign a widespread protective role to RVT as an AO. Other mechanisms in which the drug is involved include cell signaling, apoptosis and gene expression. The dichotomy of the AO RVT also exhibiting pro-oxidant action is addressed and rationalized. Another important aspect is the finding that RVT has been shown to produce no adverse effects, even when consumed in high concentrations.[1] Hence, it exhibits good protection for use in therapy for various diseases.

Reviews demonstrate the widespread involvement of ROS-OS in cancer and toxicity associated with many illnesses. The preponderance of bioactive substances and their metabolites incorporate ET functionalities, which, we believe, play an important role in physiological responses. The main groups include quinones (or phenolic precursors), metal complexes (or complexors), aromatic nitro compounds (or reduced hydroxylamine and nitroso derivatives) and conjugated imines or iminium species. In vivo redox cycling with oxygen can occur giving rise to OS through generation of ROS, such as hydrogen peroxide, hydroperoxides, alkyl peroxides, and diverse radicals (hydroxyl, alkoxyl, hydroperoxyl), and superoxide. In some cases, ET results in interference with normal electrical effects, e.g., in respiration or neurochemistry. Generally, active entities possessing ET groups display reduction potentials in the physiologically responsive range, i.e., more positive than -0.5 V ET, ROS and OS have been increasingly implicated in the mode of action of drugs and toxins (toxicants) e.g., antiinfective agents,[2] anticancer drugs,[3] carcinogens,[4] reproductive toxins,[5] nephrotoxins,[6] hepatotoxins,[7] cardiovascular toxins,[8] nerve toxins,[9] mitochondrial toxins,[10] abused drugs,[11] ototoxins,[12] pulmonary toxins,[13] immune system toxins,[14] and various other categories of drugs and toxins, including human illnesses.[15]

There is a plethora of experimental evidence supporting the OS theoretical framework, including generation of the common ROS, lipid peroxidation, degradation products of oxidation, depletion of AOs, and DNA oxidation and cleavage products, as well as electrochemical data. Of particular relevance in the present case is the prevalent beneficial effect of AOs,[16] in connection with RVT. This comprehensive, unifying mechanism is in keeping with the frequent observations that many ET substances display a variety of activities, e.g., multiple drug properties, as well as toxic effects. Knowledge of events at the molecular level can result in practical application in medicine.

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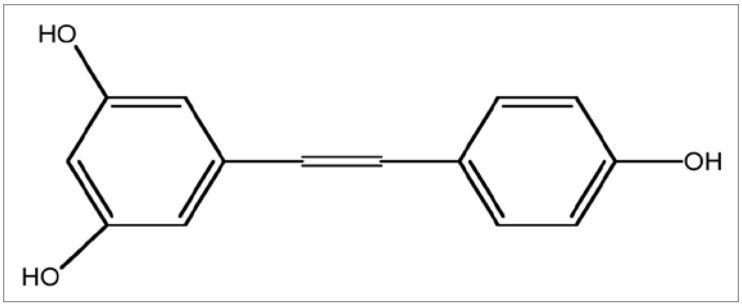

Figure 1. Resveratrol structure. The compound is a stilbene derivative containing three phenolic groups. Hence, it can exert AO action which evidently plays an important role in the protective effects observed against oxidative insult involving various body constituents. Metabolic studies show major formation of water-soluble conjugates. Many investigations deal with cell signaling pathways in the bioactivity. Particular focus has been devoted to antiaging, anti-cancer actions, cardio protection and prevention of CNS damage.

The protective effects of RVT are demonstrated for cancer and insults to many body constituents, including the cardiovascular system, central nervous system (CNS), liver, kidney, DNA and others. There is a beneficial effect in connection with aging, arthritis and inflammation. The drug is a versatile agent that also functions through cell signaling and gene expression. Other aspects treated are metabolism, receptor interaction, electrochemistry, safety and pro-oxidant behavior. Suggestions for future work are offered.

This review demonstrates that the ET-ROS-OS-AO unifying theme, which has been successful for many other classes of drugs and toxins, can also be applied to RVT, and this comprises the first comprehensive, mechanistic review devoted to that agent. However, it should be emphasized that physiological activity of endogenous and exogenous substances is often complex and multifaceted. Our objective does not encompass extensive treatment of all other modes of action. The citations are usually representative, rather than exhaustive. A number of original references may be found in the reviews and articles cited.

Metabolism

A common metabolic route for phenols involves oxidation to catechols or hydroquinones with subsequent conversion to o- or p-quinones. An ensuing result is often redox cycling entailing oxygen with production of ROS. It is quite significant that finding comparable literature for phenolic RVT is difficult. A rationale is provided by various metabolic reports. Rapid metabolism leads to about 75% excretion in urine and feces in the form of RVT glucuronides and sulfates.[17] The following conjugates are reported: 3-O-and 4'-O-glucuronides;[18] most abundant, 3-O-glucuronide and 3-sulfate;[19] main metabolites, monoglucuronide, dihydro monosulfate, monosulfate and dihydro RVT;[20] 3-sulfate, 4'-sulfate, 3,5-disulfate, 3,4'-disulfate, 3,4',5-trisulfate, 3-glucuronide and aglycone.[21] In a study with two cell lines, RVT-3-sulfate was identified.[22] The absence of toxic effects apparently results from preferential conjugation, rather than appreciable oxidation to ET quinones.

The parent RVT could act as an AO, similar to the familiar phenolic AO vitamin E. Also, the conjugates possessing free phenolic groups might exert AO effects provided contact is made with free radical species. However, conjugation with highly hydrophilic groups results in increased water solubility. An AO analog would be water soluble vitamin C.

There is scant literature on oxidative metabolism of RVT. In a metabolic study, mention is made of hydroxylation, in addition to glucuronidation, sulfation and hydrogenation.[23] Oxidation catalyzed by lipoxygenase yields a complex mixture of decomposition products, similar to those obtained with hydrogen peroxide.[24] Quinones, apparently not yet identified, may be formed in low yield, difficult to isolate due to reaction with protein nucleophiles. However, only small amounts are required to carry out catalytic ET with generation of large quantities of ROS.

Antioxidant

The AO property is apparently an important aspect of the physiological activity of RVT, particularly in relation to protection from oxidative injury. The literature is extensive and is also cited in other parts of this review.

The AO effect of RVT was manifested in blood mononuclear cells by a significant reduction in malonaldehyde content, an indication of oxidant injury.[25] The cells acquired AO capacity. Grape RVT may be a useful dietary supplement for minimizing oxidative injury in immune-perturbed states and human chronic degenerative diseases. The effect of RVT on oxidative/nitrative stress by peroxynitrite, which is a strong physiological oxidant and inflammatory mediator, was determined in human blood platelets.[26] Protein oxidation was significantly inhibited. Oxidation of thiol groups in protein and GSH was markedly reduced. There was distinct reduction in platelets lipid peroxidation. Various protective effects against peroxynitrite induced oxidative/nitrative damages to human platelet proteins and lipids were observed. RVT reduces OS induced by cisplatin and Se-Pt in human blood platelets, lymphocytes and plasma.[27] The AO decreased lipid peroxidation and reduced activities of anti-oxidative enzymes, such as SOD, catalase and GSH peroxidase. A significant decrease in DNA damage was observed. Another study dealt with the antioxidation and free radical scavenging activities in the protective effects on ischemia-reperfusion induced injuries of rat hearts.[28] Scavenging of the stable free radical DPPH was also observed. Astringinin, a more water soluble catechol-type analog, has a superoxide scavenging ability about 160 times more potent than that of RVT, and, hence could potentially be used as an AO and cardioprotective agent in biological systems. The efficiency of RVT for protecting polyunsaturated fatty acids was higher than that of flavonoids during oxidation.[29] A related study deals with inhibition of human LDL oxidation by RVT.[30] The phenol exhibits potent AO properties related to anti-inflammatory and anti-catabolic effects.[31] The findings suggest possible application of RVT in therapy of human and animal osteoarthritis.

RVT could be a useful drug for the protection of liver cells from OS induced damage.[32] The phenol is of interest for its beneficial properties in a variety of pathologies, including neurodegeneration.[33] Many of the beneficial effects have been attributed to the ability to reduce OS. Bioactive phenols, such as RVT, can quench ROS and thus avoid pro-oxidative damage.[34] This highly effective protection against OS damage suggests that this AO property constitutes the major part of preventing tumor induction. An investigation was made of the mechanism of cardioprotection by RVT in ischemia-reperfusion.[35] The protection of cardiomyocytes from injury occurs partly by suppression of superoxide levels via AO action.

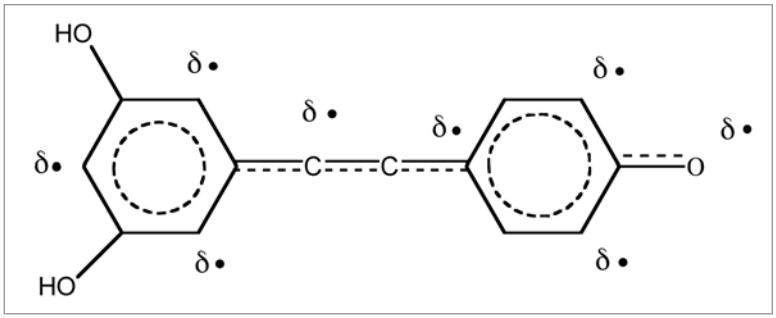

Figure 2. Resveratrol radical. The illustrated phenoxy radical is generated during the widespread AO action of RVT. The radical formation is facile due to the high degree of resonance stabilization afforded by this species. Hence, energetically, this radical is favored over the ones that would be formed from the meta-hydroxy resorcinol group in the other ring. Radical propagation is terminated by C-C radical coupling leading to a more stable dimer.

The mechanism of phenolic AO action has been addressed in a recent book.[16] A key step is stoppage of radical propagation by formation of a resonance-stabilized peroxy radical, shown in **Figure 2** for RVT. A report deals with mechanism and efficiency of AO action involving RVT and analogs.[36] The comparison of the radical-scavenging effects of RVT and its analogues trans-4-hydroxystilbene and trans-3,5-dihydroxystilbene revealed that the two analogs showed almost the same effect and were more efficient than trans-3,5-dihydroxystilbene. These findings indicate greater radical-scavenging activity of the trans-resveratrol para-hydroxy group than its meta-hydroxy groups. Other data showed great similarity between RVT and trans-4-hydroxystilbene which seems to confirm that the para-hydroxy group of trans-resveratrol scavenges free radicals more effectively than its meta-hydroxy groups. The results can be rationalized by the greater delocalization possible for the radical from the para hydroxy group vs. the meta analog. Another important aspect entails termination of radical propagation by the phenoxy radical. This favorable aspect involves conversion to non-radical product by C-C coupling.[16] This process is reported to occur with the radical derived from RVT.[37] Trapping of the radical occurs by dimerization yielding trans-delta-viniferin which is unable to chain propagate.

Cell Signaling

An investigation was made of the regulatory effect of RVT on signal transduction pathways in leukemia.[38] Data indicate reduction in activation of JAK1/STAT3 tyrosine phosphorylation, as well as downregulation of expression. Evidence indicates activation of the Raf/Ras cascade and reversal of the sustained phosphorylation of JNK/SAPK.[39] The study deals with the effect of RVT on signal transduction pathways involved in paclitaxel-induced apoptosis. The phenol inhibits phorbol ester activation of JNK and PKC.[40] The inhibition may have a therapeutic potential, perhaps providing a novel means of controlling growth and invasiveness of tumors. A report deals with RVT modulation of phorbol ester-induced signal transduction pathways leading to elevated COX-2 expression.[41] Other signals involved are NFkappaB, MAP kinases, AP-1 and protein kinase (ERK). An overview summarizes RVT modulation of signal transduction in apoptosis and cell survival.[42] There is interference with many intracellular signaling pathways which regulate cell survival and apoptosis. Further insight is provided into the signaling network and interaction points. A review discusses the diverse molecular targets with focus on those involved in intracellular transduction.[43] RVT impacts many components of intracellular signaling pathways including regulation of apoptosis and cell survival, tumor switches involved with kinases, transcription factors and their regulators. Evidence indicates that the stilbene derivative targets PTPIB to inhibit PDGFR mitogenic signaling.[44] RVT mediates its effects through modulation of many different pathways by binding to numerous cell-signaling molecules.[45] The compound activates various transcription factors, e.g., NFκB, STAT3, HIF-1α, β-catenin and PPAR-γ, suppresses the expression of antiapoptotic gene products, inhibits protein kinases, e.g., src, P13K, JNK and AKT, induces AO enzymes, and modulates cell cycle regulatory genes. The polyphenol holds promise against numerous age-associated diseases. An investigation was made of signaling pathways influenced by RVT involved with apoptosis and growth control in leukemia.[46] Apoptosis is induced by modulating three different signaling pathways that regulate cell death and survival. The survival signaling pathway Notch is inhibited. The phenol inhibits P13K/Aket and activates Gsk/3β. Pro-apoptotic proteins p53 are also influenced. RVT reduces paclitaxel-induced apoptosis by modulating cell signaling pathways.[39]

Since the literature on cell signaling involving RVT is voluminous, additional, representative material is provided in abbreviated form. The organ or action is indicated along with the cell signaling involved in **Tables 1–5**.

In relation to mechanism at the basic level, recent proposals focus on ROS and electrochemistry. Cell signaling is known to be importantly involved in various aspects of biological function, including normal processes, therapeutic drug action and toxicology. More than 10 years ago, ROS attracted attention in relation to cell signaling. Since then several books[103,104] and a book chapter[105] have addressed this aspect. A recent review has further insight.[106] Evidence has accumulated that ROS, such as hydrogen peroxide, superoxide, and the hydroxyl radical, are important chemical mediators that regulate the transduction of signals by

Table 1. Apoptosis

Cell signaling agent	Organ or action	Reference
(1) MAP kinases	Human breast cancer cell MCF-11	47
(2) Fas redistribution in the rafts	Colon cancer cells	48
(3) Ceramide	Breast cancer cells	49
(4) STAT3 and nuclear factor-κB-regulation	Human multiple myceloma cells	50
(5) Protein kinases and p38 kinase	Antitumor activity	51
(6) Src and Stat3	Breast cancer	52
(7) TRAIL-induced	Mitochondria	53
(8) Phosphorylated Akt and Caspace-9	MCF7 human breast cancer cells	54
(9) Cdc42 activation of ASK1/JNK	Human leukemia cancer cells	55
(10) Phosphatidylinositol 3'-kinase Akt	Human prostate cancer cells	56
(11) WAF-1/p21-mediated G_1 phase	Human epidermoid Carcinoma A431 cells	57
(12) AMPK	Colon cancer cells	58
(13) JNK and c-JUN/AP-1	Prevented HNE-induced JNK	59
(14) c-Myc	Downregulation in human medulloblastoma	60
(15) ERK	Initiates p53 dependent apoptosis via αVβ3	61
(16) Caspase-3	Human breast cancer cell	62
(17) CD95	Human tumor cells	63
(18) TNBS	Inhibiting Notch pathway	64
(19) p53 and P13K/Akt	Human T-cell acute lymphoblastic leukemia MOLT-4 cells	65

Table 2. Cancer

Cell signaling	Organ or action	Reference
(1) NFκB and Ap-1	Genes	66
(2) p38, MAPK, p53 and p21	Cancer cells	67
(3) NFα mediated MMP-9 expression	Hepatocellular carcinoma cells	68
(4) TRAIL through gene expression	Human melanomas	69
(5) STAT3	Medulloblastoma cell lines	70
(6) MAPK	Breast cancer cells	71
(7) c-Jun-NH2-terminal-kinase	Waldenström's macroglobulinemia	72
(8) NFκB	Cardiovascular, neurological and mitochondrial dysfunction	73
(9) ATM/ATR-Chk1/2-Cdc42	Ovarian cancer cells	74
(10) Rac and Cdc42	Breast cancer cells	75
(11) P13K	Cultured muscle cells	76

modulating protein activity via redox chemistry. Authors have proposed that ROS have been conserved throughout evolution as universal second messengers. Nearly every step in signal transfer is sensitive to ROS, which can function as second messengers in the activation of transcription factors. Various types of radiation, which are generators of ROS, also influence cell communications. Since the messengers must possess appreciable lifetime in order to migrate, a certain degree of stability is required. For example, the hydroxyl radical would not be a messenger due to its extremely high reactivity with its resultant very short time existence, although it would generate messenger radicals. Likely candidates include superoxide and resonance stabilized peroxyl radicals. Others would be stable ROS arising from AOs, such as vitamin C, vitamin E and flavonoids. Members can be envisioned from the reactive nitrogen species (RNS) category. NO is a well known radical that plays an important role in cell signaling. In relation to theory, a puzzling aspect is its relatively short life time. Perhaps more stable complexes are involved. Other nitrogen radicals can play a role. Important candidates comprise small proteins possessing redox groups.

In effect, cell signaling can be regarded as proceeding via a long redox chain in which the standard parameters of initiation, propagation and termination pertain, involving omnipresent conduit species with unshared electrons. A series of relay stations may be operative. Based on the redox chain framework, the second messenger might be superoxide formed by redox process involving oxygen and a second messenger electron from an ET functionality in the receptor site. At the termination of the initial journey, radical character would be transmitted to a site, mobile or stationary, e.g., a redox amino acid (AA) side chain acting as a relay (transfer station), that could then pass on (initiate) radical character to a third messenger. These types of interactions, widespread in AA chemistry, usually involving electron and/or hydrogen abstraction to generate radical species, are treated in a review.[107] The numerous redox moieties in anchored proteins might fall in the relay category. There has been dramatic increase in attention devoted to free radical species in cell signaling, although the bulk of the signal transduction literature pays no attention to this aspect.

Electrochemistry also appears to play a role in cell signaling, including electron transfer and electrostatics. Discussion is present in recent reviews on receptor-ligand activity,[108] phosphates and sulfates[109] and metal cations.[110]

Receptors

The literature on the RVT receptor is very limited. RVT is a phytoestrogen which binds to and activates estrogen receptors that regulate the transcription of estrogen-responsive target genes.[111] The effect on gene expression appears to correlate with chemoprevention. The drug regulates mRNA expression of several genes involved in cell cycle control, apoptosis, metastasis, cell-cell adhesion and receptor signaling pathways. A report shows RVT binds to the sulfonyl urea receptor.[112] Electrophysiological measurements revealed that the bound ligand is a blocker of pancreatic SUR channels and enhances apoptosis. RVT is known to

influence the androgen receptor (AR). AR pathways are involved in the development and progression of prostate cancer.[113] The ability to modulate AR function may contribute to the chemopreventive activity of RVT. Also, the drug regulates AR target gene expression, at least in part, by repressing AR transcriptional activity.[114,115] RVT represses different classes of AR. AR upregulates genes at the protein or mRNA level, and may be a useful preventive or therapeutic agent for prostate cancer.[116] Aryl hydrocarbon receptor ligands, such as dioxin and polynuclear aromatic hydrocarbons, are environmental contaminants with many adverse effects.[117] RVT, a competitive antagonist of these ligands, promotes receptor translocation to the nucleus and binding to DNA. The phenol inhibits the transactivation of several dioxin-inducible genes. Clinical testing as a prophylactic against the insults is warranted.

Electrochemistry

Glucose-induced depolarization was counteracted by RVT.[118] There is inhibition of electrical activity and insulin release from insulinoma cells by blockage of voltage-gated Ca channels and chloride currents, with inhibition of K (ATP) currents. RVT inhibits the electrical activity of paraventricular nucleus neurons and exerts neuroprotective effects on central neurons.[119] The effects of RVT on neuron discharges in rat subfornical organ were examined.[120] The inhibition of electrical activity may be related to blockade of voltage-gated Ca channels and NO promotion. A study demonstrated RVT-induced depression of electrical activity in the rat heart.[121] The shortened action potential in the left atrium is likely due to activation of K (ATP) channels. The importance of electrochemistry in living systems has been reviewed recently.[122]

Aging

The anti-aging property of RVT has enjoyed much attention. This aspect is also addressed in many other portions of this review. Considerable prior literature identifies ROS with the aging process.

An article deals with prevention and treatment of common clinical conditions of aging.[123] Aging is associated with a variety of common conditions, such as cancer, diabetes, cardiovascular disease and Alzheimer's disease. Properties of the phenol associated with the beneficial aspects include AO, regulation of the cell cycle, activation of intracellular pathways, vascular tone, oncogene suppression and mitochondrial energy production. There is a striking transcriptional overlap of RVT and calorie restriction in the heart, skeletal muscle and brain.[124] Both interventions inhibit gene expression associated with cardiac and skeletal muscle aging, as well as prevention of cardiac dysfunction. RVT fulfills the definition of a dietary compound that mimics some aspect of calorie restriction. A review summarizes the anti-aging properties of RVT, including cardiovascular benefits via increased NO production, downregulation of vasoactive peptides, lowered levels of oxidized low-density lipoprotein, cyclooxygenase inhibition, effects on neural tissues, phytohormonal actions, anticancer properties via modulation of signal transduction (anti-initiation, antipromotion and antiprogression effects), antimicrobial effects, sirtuin activation, possible benefits in Alzheimer's disease and prevention of photoaging.[125] Comparison was made with other AOs used in skin care products. RVT consistently retards aging in organisms as diverse as yeast, worm, fly and fish.[126] It prolonged lifespan and delayed the onset of age-related dysfunctions in fish. A review focuses on the role of OS and inflammation in cardiovascular dysfunction in aging, and on emerging anti-aging therapeutic strategies offered by RVT and other polyphenols.[127] In a study of RVT influence on aging, the drug mitigated the metabolic dysfunction of mice fed high-fat diets.[128] The effects may be mediated partly by activation of a deacetylase enzyme that regulates several transcription factors and enzymes responsive to nutrient availability.

Table 3. Inflammation

Cell signaling agent	Organ or action	Reference
(1) NFκB	Chromatin structure Glutathione biosynthesis	77
(2) IL-6-induced ICAM-1	gene expression in endothelial cells	78
(3) P13KK/AKt/ERK dependent interleukin IL-17	Mouse cardiac fibroblast	79
(4) TNFα	Endothelial cells	80
(5) Cytokine 1L-1β	Human chondrocytes	81
(6) NFκB and AP-1	Mouse skin cell	82
(7) TLR-derived	Mouse embryonic fibroblast	83

Cancer

Antioxidant. OS arising from ROS appears to be associated with many aspects of carcinogenesis.[4] For example, there is involvement in three major stages of the process. Literature cited[129-134] indicates that RVT as an AO provides a beneficial effect in alleviation of harmful OS. In some cases, there is evidence for significant modulation of oxidative imbalance and effect on levels of other AOs.

Apoptosis. Apoptosis plays a part in many aspect of biological chemistry. There are many articles which deal with it in connection with cancer. The reports addressed herein do so in connection with presence of RVT.[62,135-149]

Cell signaling. This aspect has been addressed in a general approach (see above). Cell signaling has played a role in many aspects of biochemistry. It is not surprising that considerable attention has been devoted to its relationship with cancer. Mechanistic aspects of signaling are summarized in an above section. Representative articles are provided that involve RVT.[43,58,150-158]

Nitric oxide. This fascinating gas possesses a wide variety of bioactivities, both beneficial and deleterious. Many modes of action have been implicated. One review puts focus on electron transfer.[159] Peroxynitrite formed by reaction with superoxide,

Table 4. Heart

Cell signaling agent	Organ or action	Reference
(1) AMPK	H9c2 cardiac muscle cells	84
(2) NFκB	Endothelial cells of coronary artery	85
(3) p38 and ERK/1/2	Inhibits EMMMPRIN THP-1 cells	86
(4) p38 Mitogen-activated protein kinase	Triggers an MAPK path involving ERK ½ and P38 MAPK	87
(5) Bcl-2	Adenosine A_3 receptor Activation	88
(6) p38 map kinase and P1-3-kinase	HO-1 mediated mechanism	89
(7) Akt/protein Kinase B	Suppresses angiotensin II-induced protein	90

Table 5. Miscellaneous

Cell signaling agent	Organ or action	Reference
(1) NF-E2	HO-1 gene expression	91
(2) Kinase	Reduces oxidation of human retinal pigment epithelial cells	92
(3) AMPK	Antidiabetic	93
(4) Nrf2	Cigarette smoke-mediated OS	94
(5) SIRT1 and AMP kinase	Human alcoholic liver disease	95
(6) Ras	Stimultes sirtuins and extends life span	96
(7) Caspase-3	Inhibits IL-1β-induced stimulation	97
(8) 3-Kinase/Akt	Inhibition of phosphor-inositide-dependent kinase-1 activity	98
(9) NFκB	Stimulates cytokines IL-6-1β and NFκB	99
(10) P13K	Inhibition	100
(11) AMP kinase	Stimulate AMPK in neurons	101
(12) NFκB and AP-1	Activate and regulate gene expression	67
(13) MAPK	Activate through estrogen receptors	102
(14) NFκB, STAT3, HIF-1α	Activate transcription factors	45

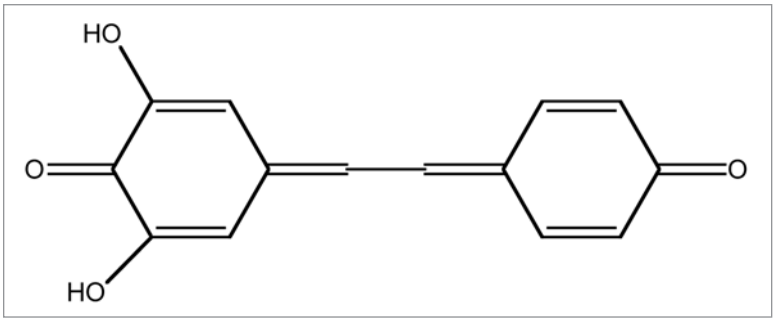

Figure 3. Resveratrol quinone. This stilbene quinone would be expected from facile oxidation of RVT. However, we are unable to find any report of its formation. It may be that it is present only in very small amounts making for greater difficulty in isolation. Nevertheless, only minor quantities will suffice for the catalytic generation of large amounts of ROS. Quinone formation is one rationale for the observed pro-oxidant effects of RVT involving redox cycling with oxygen leading to ROS.

plays a role, particularly in toxicity. A sampling of literature is presented for the effects of NO along with RVT.[135,160,161]

Miscellaneous aspects. There are many other approaches that deal with the cancer problem, along with involvement of RVT.[162-174] Examples involve hormones, polyamines, autophagy, cathepsin D, DNA synthesis and mitochondria.

Cardiovascular System

RVT displays many bioactivities, such as protection from or reduction of the incidence of coronary heart disease, including counteraction to ischemia-reperfusion injury.[175] It might be that there is inhibition of signaling pathways and gene expression which involve the disruption of the ERK pathway via attenuation of ROS. A review focuses on the role of the phenol on OS and inflammation in cardiovascular disease.[176] Intake may contribute to the "French paradox" involving the unexpectedly low cardiovascular morbidity in the Mediterranean population, which may reflect the AO and anti-inflammatory effects. Upregulation of NO production might also be involved.[177] The amount of malondialdehyde, indicative of lipid peroxidation, was decreased in the postischemic myocardium indicating a reduction of OS.[178] There was prevention of superoxide-dependent inflammation response induced by ischemia-reperfusion and oxidants.[179] AO properties may be involved. RVT exhibits multifaceted properties in preventing various harmful vascular alterations, in addition to aging, including cell signaling, enzymatic pathways, apoptosis, gene expression and AO action.[180] The review discusses the relationship with ROS and regulation of pro-inflammatory genes. Administration of RVT exerts cardioprotection against ROS-mediated menadione toxicity.[181] Results indicate that the drug interferes with the release of inflammatory mediators, thus providing biological plausibility to the protective effect of moderate red wine consumption against coronary heart disease.[182] In a related study a protective AO effect of RVT in red wine was demonstrated against oxidative injury on red blood cells.[183] Authors proposed that the AO and antiapoptotic effects, together with the anti-inflammatory actions, are responsible, at least in part, for the cardioprotective effects.[184] Upregulation of endogenous AOs and certain enzymes by red wine RVT in aortic muscle cells leads to protection against oxidative and electrophilic stress.[185] Various investigations dealt with the effects on blood platelets, such as, action as AO for reduction of OS,[186]

inhibition of superoxide generation, ROS production and lipid peroxidation.[187] The drug reduces ROS levels, blunts the inflammatory pathways and stimulates NO generation.[188] There is inhibition of ROS production, e.g., superoxide, hydrogen peroxide, singlet oxygen and organic radicals,[189] and a variety of actions including anti-inflammatory, AO, ROS, scavenger and reduction of lipid peroxidation.[190]

A prior comprehensive review on prevention of cardiotoxicity is based on the unifying theme of ET-ROS-OS.[8]

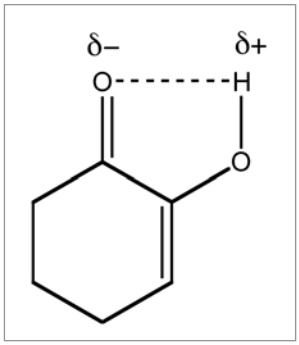

Figure 4. Enol tautomer of cyclohexane-1,2-dione. Although the keto form is generally favored over the enol tautomer, in the case of "4," hydrogen bonding of enol with the carbonyl results in increased contribution of enol to the equilibrium state.

Central Nervous System (CNS)

Much research supports the thesis that ROS play a role in insults to the CNS.[9] Since the brain is deficient in defenses by AOs, supplementation should be investigated as a potential clinical approach. There are many reports demonstrating the beneficial effect of RVT in preventing toxic attacks in relation to brain neuronal injury in conditions such as Alzheimer's disease and Parkinson's disease.[191-199] In many cases, attribution is given to the AO property. In the treatment of traumatic brain injury, the drug provided neuroprotection by reducing OS.[200] There is a related report.[201] Increased OS has been implicated in the mechanism of neuronal cell death following cerebral ischemic insult.[202,203] RVT exerted a protective action, apparently as an AO. The phenol is a potent neuroprotective agent against diabetic oxidative damage.[204] There was reduction in lipid oxidation product and NO production, as well as OS and DNA fragmentation.[205] A neuroprotective effect via free radical scavenging was observed with induced Parkinsonism.[206,207] Intervention by AOs can be a potential beneficial approach in the treatment of epilepsy.[208] The protective effect of RVT against kainic acid-induced convulsions and the attenuation of lipid oxidation product suggest the potential use of AOs as adjunct therapy in epilepsy. The neuroprotective ability of RVT against NO-related toxicity in hippocampal neurons is attributed to AO involvement.[209] Also, a neuroprotective effect was observed in cerebral ischemia.[210] There was decrease in product from lipid oxidation and induction of an important role for NO.

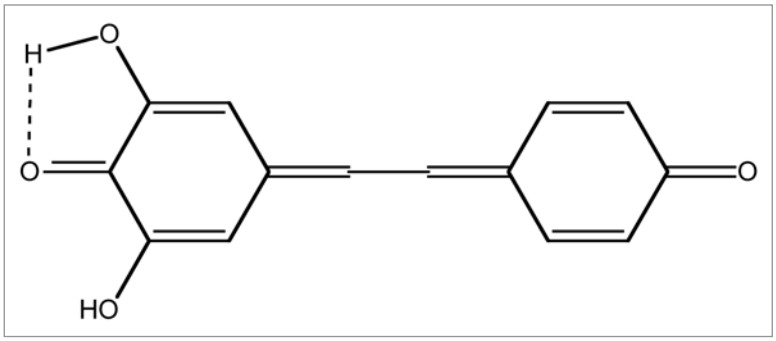

Figure 5. Mono-hydrogen bonded quinone. This structure is analogous to that in Figure 4. Hence, the enol moiety is stabilized.

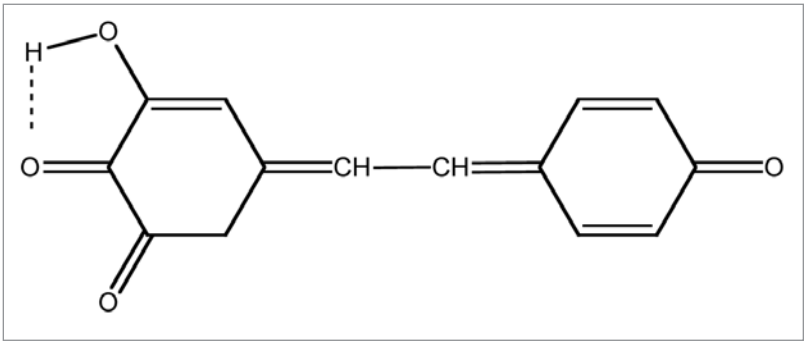

Figure 6. Diketo-enol tautermer of "3" (Fig. 3). Structure "5" (Fig. 5) shows the stabilization of an enol group by H-bonding, similar to that in "4" (Fig. 4). Since this is now less likely for the other enol group. It may tautomerize mostly to the keto form as illustrated in "6" (Fig. 6). The ability to redox cycle would be substancially decreased due to absence of the quinone functionality. The conjugated α-dicarbonyl structure in "6" (Fig. 6) should be capable of electron uptake, but not be a good generator of ROS.

Inflammation

An appreciable amount of research is reported on the anti-inflammatory effects of RVT. Evidence shows that the condition is associated with the presence of ROS.[15] Hence, it is not surprising that the powerful phenolic AO exerts a beneficial effect. Literature in the area is also discussed elsewhere in this review, such as in cell signaling.

Some research in this area involves the lungs.[211] With human airway epithelial cells, RVT inhibits NFκB-protein dependent transcription and cytokine-stimulated inducible NO synthase cells. The salutary effects of the drug on attenuation of lung injury following trauma hemorrhage are likely due to reduction of pro-inflammatory mediators.[212] Plausible mechanisms of anti-inflammatory activity are discussed.[213] This property may have relevant clinical implications. The drug could alleviate the

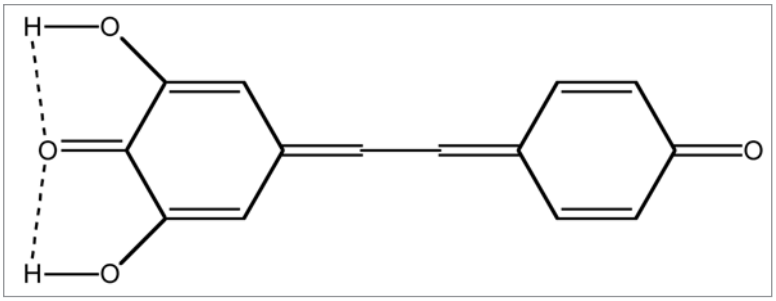

Figure 7. Di-hydrogen bonded quinone. Perhaps both enols participate in H-bonding with the carbonyl. Therefore, the quinone structure is maintained.

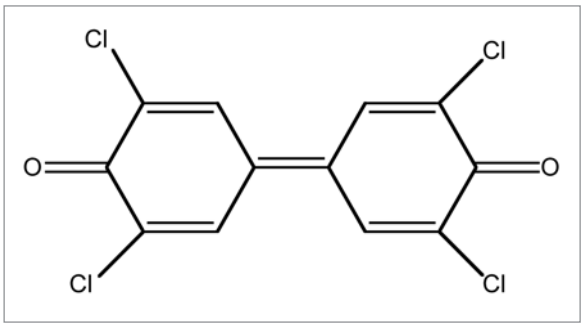

Figure 8. Quinone metabolite of PCB. This metabolite route to "8" is quite similar to that proposed for RVT, which provides support for the proposed oxidative metabolism. The monohydroxy metabolite of PCB is analogous to RVT.

severity of pancreatitis through its anti-inflammatory effects, regulation of inflammatory mediators and inhibition of NFκB expression.[214] Also, there is prevention of superoxide-dependent inflammatory response induced by ischemia/reperfusion platelet-activating factor or oxidants.[215] The phenol decreases the degree of inflammation associated with colitis.[64] The effect may result from the countering of OS and proinflammatory cytokines. Attenuation of ischemia/reperfusion injury in rats is due to the ant-inflammatory action of RVT, apparently through a NO-dependent mechanism.[216]

Arthritis

Much evidence supports a role for ROS-OS in arthritis.[15] This includes oxidative damage to DNA, protein and lipids. In accord with involvement of ROS, there is depletion of GSH, ascorbate and α-tocopherol. Hence, it is not surprising that the AO RVT possesses the potential for arthritis treatment.[217] Inflammation, which is commonly associated with arthritis, appears to have a ROS link.[15] Involvement of cell signaling pathways is also treated.[217] The inflammatory process plays a pivotal role during the pathogenesis of osteroarthritis, dominated by catabolic processes initiated by pro-inflammatory cytokines, such as IL-1 beta.[218] RVT appears to be an effective anti-inflammatory agent that has a chondroprotective capacity through suppression of IL-1β, ROS and tumor suppression protein p53 production. NFκB is a pivotal transcription factor involved in the activation of the TNFα and IL-β genes.[219] Activation of NFκB is a feature seen in arthritis patients. RVT is a potent and specific inhibitor of TNFα and IL-1β. Injection of the drug may protect cartilage against the development of inflammatory arthritis.

Liver

Pyrogallol causes hepatotoxicity in experimental animals.[220] RVT reduces the increase in lipid peroxidation due to OS by the toxicant. The accompanying decrease in GSH, GSH peroxidase and GSH reductase activities was significantly attenuated by the phenol. In a study of the liver damage with a high-fat diet, RVT reduces oxidized LDL and hepatic OS.[221] RVT-mediated chemoprevention of hepatocarcinogenesis occurred with nitrosamine-initiated carcinogenesis.[222] The favorable effect was attributed to inhibition of cell proliferation and induction of apoptosis. A review documents evidence for the favorable effect entailing destruction of cancer-initiating ROS by AO action (see Introduction). Liver damage caused by chronic alcohol consumption was reduced by RVT.[223] Inhibition of oxidation of polyunsaturated fatty acids is proposed as a basis of the hepatoprotective effect. The involvement of OS in the pathogenesis of alcoholic diseases in the liver has been repeatedly confirmed.[224] Dietary supplementation with RVT during ethanol treatment inhibited hepatic lipid peroxidation and ameliorated the reduction in activity of SOD, catalase and GSH peroxidase.

Kidney

The protective effect of the AO resveratrol and others was investigated in the kidney of rats treated with the carcinogen $KBrO_3$.[225] The 100% increase in 8-OH-dG from oxidation in the renal genome DNA was completely abolished by treatment with RVT. ROS have been implicated in cell injury that occurs after ischemia.[226] Products of lipid peroxidation are generated on reperfusion. This oxidation can be prevented by AOs. Resveratrol was found to exert a favorable effect in reducing such injury. A related report is available.[227] An hypothesis was advanced concerning the beneficial effects of red wine which contains resveratrol.[228] Evidence suggests a protective role of moderate wine consumption against the onset and progression of renal diseases, based on the concept of kidney injury mediated by OS. A similar study was reported.[229] ROS are observed in gentamicin-induced nephrotoxicity.[230] Renal lipid peroxidation increases with the toxicant alone, which was prevented by the administration of RVT.[230] Addition of the phenol resulted in an increase in the levels of AOs. At least a part of the favorable effects was attributed to the AO activity.

DNA

RVT reduces nuclear DNA fragmentation.[231] Results indicate that the drug can act as an antimutagenic/anticarcinogenic agent

by preventing DNA damage which plays a pivotal role in the carcinogenic activity of many genotoxic agents. The phenol reduced DNA damage induced by Cr (III) based on reduced 8-OH-dG formation.[232] The protective effect against Cr-induced carcinogenesis may relate to the free radical-scavenging ability. The genoprotective effects of the drug were investigated under conditions of OS induced by hydrogen peroxide in glioma cells.[233] Due to attenuation of oxidative DNA damage, RVT may be important in protecting against DNA fragmentation and oxidation arising from OS. In a study of Alzheimer's disease, red wine micronutrients were found protective. The phenols reduced ROS production, prevented DNA fragmentation and protected the cellular membrane from oxidative damage.

Genes

RVT significantly blocked the expression of genes related to the NFκB family.[234] The phenol has a significant modulatory effect on the NFκB signaling pathway and an important AO role that may help explain the cardioprotective effects attributed to long-term moderate red wine consumption. Through its phytoestrogenic properties, RVT regulates the expression of hormone-dependent genes in breast cells and provides a protective effect against several types of cancer, notably breast cancer.[111] The drug modulates the expression of genes in a pattern dependent on the state of estrogen receptors. Gene expression is regulated via the estrogen receptor pathway and also an undetermined pathway. The effects of RVT on circadian clocks of Rat-1 cells were analyzed.[235] A dose, which did not exhibit toxicity, regulated the expression of various clock genes. Relevant material is also present elsewhere in this review.

Other Body Constituents

In addition to the extensive studies presented in the above sections, there are many reports of the beneficial effects of RVT on other body constituents under stress. Much of the salutary responses can be attributed to AO action under OS. RVT limited dysfunction of rat brain mitochondria in an anoxia-reoxygenation model.[236] At least three mechanisms were proposed, including AO properties. Data indicate that the drug may have application in the treatment of bronchial asthma, accompanied by inhibition of increases in cytokinases.[237] A review provides evidence for AO protection of various pulmonary disorders.[13] The phenol exerted beneficial activity against alcohol injury, e.g., peroxidation of lipids.[238] The adverse effects, countered by AO action involve ROS and OS. Oxidative stress entailing rapid degeneration of endothelial cell function, is deeply involved in systemic sclerosis pathogenesis.[239] There is potential for RVT as an AO for reverting endothelial dysfunction, scavenging lipid peroxides and reducing hypoxia-reperfusion injury. Examination revealed a significant improvement in ovarian morphology in RVT-treated rats, compared with the ischemia-reperfusion group.[240] Drug administration reduced lipid peroxide products and countered the reduction in GSH levels. The phenol exerted a favorable influence against lipid peroxidation in cell membranes, including a decrease in DNA damage.[241] An important AO role was assigned. Also, an inhibitory effect was observed on the NFκB signaling pathway after exposure to metal-induced radicals. Obesity in the US has become a serious problem, leading to a sharp increase in diabetes. In a controlled study, RVT treatment caused the greatest and most consistent loss of fat content in animal subjects.[242] The underlying target protein likely involves sirtuin family members. A study was carried out involving RVT and Cd-induced oxidative damage in mice.[243] The phenol and other AOs effectively protect against lipid peroxidation generated by the metal, and were able to counter the inhibition of catalase activity. Metals are well-known generators of ROS and OS.[2-15]

Skin cancer is a common illness among humans, due to solar radiation.[243] A way to reduce the occurrence is by use of photochemopreventive agent, often in the AO category.[244] Results suggest that RVT may afford substantial protection against damage caused by UVB exposure, which may be mediated via its AO properties. RVT reduces colitis, alleviates oxidative events and stimulates apoptosis.[245] Much attention has recently been paid to nanoparticles. RVT-loaded nanoparticles protected cells from β-amyloid peptide toxicity by attenuating intracellular OS and caspase-3-activity.[246] A review addresses various approaches to immunomodulation.[247] Disruption of the accompanying proinflammatory cascade is by various therapies, including RVT, involving various mechanisms, including AO effects and alterations in cell signaling.

Pro-Oxidant

The literature contains extensive documentation for AO action by RVT as presented above. However, there is an apparent dichotomy based on an appreciable number of reports providing evidence for pro-oxidant action. The following material addresses these references, followed by rationale for the dichotomy.

Compounds, such as RVT, acting as AOs to lipids often have a pro-oxidant effect on DNA or protein.[248] Free radicals derived from the phenol appear to mediate between anti-and pro-oxidative actions. Dietary polyphenols with phenol rings are metabolized by peroxidase to form pro-oxidant phenoxy radicals which are sufficiently reactive to co-oxidize GSH or NADH accompanied by extensive oxygen uptake and ROS formation.[249] The experimental conditions are important for the pro-oxidant activity, causing oxidative DNA damage that may lead to cell cycle arrest or apoptosis.[250] At certain concentrations, RVT elicits pro-oxidant properties as evidenced by an increase in intracellular superoxide.[251] The pro-oxidant effect is further supported by other observations. An unusual study reveals opposite effects on rat tissue lipid peroxidation.[252] With a dark-light cycle, RVT behaved as an AO during the dark span, and as a pro-oxidant during the light span, comprising further support for the importance of conditions.

Discussion of the AO-pro-oxidant aspect is available for other well-known AOs, such as vitamins E and C, flavonoids and thiols.[16] For the phenols, a pro-oxidant appears to involve conversion to a quinone capable of ET-ROS-OS. A similar route would apply to RVT in relation to oxidation to the stilbene quinone "3" (**Fig. 3**). However, we have not found such a report (see Metabolism

section). It may be that the quinone has not yet been isolated due to formation in small quantities with much being tied to protein by nucleophilic attack (see Future Work).

A superficial approach might lead to assignment of quinone "3" (**Fig. 3**) as the product from oxidation of "1." However, application of basic principles of organic chemistry could lead to different conclusion. Compound "3" (**Fig. 3**) is a conjugated dienone incorporating two enol groups. Generally, at equilibrium, the keto state is energetically favored over the enol tautomer. An exception is cyclohexane-1,2-dione for which enol "4" (**Fig. 4**) makes a substantial contribution due to enol stabilization by hydrogen bonding with the carbonyl.[253] It is reasonable to apply this reasoning to "3" (**Fig. 3**) as shown in structure "5" (**Fig. 5**). On the other hand, such interaction makes similar H-bonding by the other enol less likely. As a result, the keto form shown in "6" (**Fig. 6**) could prevail. Therefore, the quinonoid structure capable of redox cycling with generation of toxic ROS would not pertain. This scenario is in line with the very low toxicity exhibited by RVT.[1] Another possibility is H-bonding involving both enol groups, as illustrated in "7" (**Fig. 7**), or conversion to an ET o-quinone via oxidation of adjacent hydroxyl groups in the tetrahydroxy precursor of "3" (**Fig. 3**).

It should be recognized that "6" (**Fig. 6**) could also be capable of electron uptake, but less efficiently than the related quinone. Compound "6" (**Fig. 6**) is a conjugated analog of diacetyl which is electron affinic, but exhibits negligible ability to generate significant OS via ROS.[253]

The placement of the hydroxyl groups apparently is beneficial due to phenolic AO action, but largely avoids the damaging redox cycling that often results from quinone generation via oxidation. This represents another example of a clever strategy employed in the biochemical domain.

Analogy can be made to metabolism of PCBs, in which oxidation proceeds via mono- and di-hydroxyl derivatives to the quinone "8" (**Fig. 8**) stage. Compound "8" (**Fig. 8**) is known to redox cycle with formation of ROS which appear responsible for some of the toxicity.[254]

An alternate interpretation exists for the pro-oxidant behavior. Phenols, including RVT, form complexes with metals. In the case of heavier metals, the favorable reduction potential can lead in vivo to redox cycling involving oxygen with formation of ROS leading to OS.[2-15] In the presence of Cu ions, DNA damage by RVT occurs which is attributed to oxidative intermediates formed by redox cycles involving the metal complex.[255] Similar studies were made.[256-261]

Future Work

A principal aspect of metabolism (see above) involves formation of conjugates. It would be helpful to ascertain whether or not the mono- and di-derivatives with at least one free phenolic group possess AO properties. A careful analysis of metabolic products from oxidation should be performed with the aim of detecting the proposed quinone. Authentic material would be synthesized for comparison. Also, it could be illuminating to oxidize **1** at the carbon between the resorcinol hydroxyl groups and determine the structure in relation to the hypothetical quinone. Computational studies should cast light on the structure of "3" (**Fig. 3**).

Other Aspects

Related articles are available, including ones dealing with antioxidants.[262-271]

Acknowledgements

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