The Impact of Reactive Oxygen Species on Anticancer Therapeutic Strategies

Wpływ reaktywnych form tlenu na antyrakowe strategie terapeutyczne

Abstract
Over 50 years of experience in free radical biology and medicine shows that normal cells of healthy mammals are characterized by a low steady-state level of reactive oxygen species (ROS) and a constant (reference) level of reducing equivalents. A lasting increase of ROS above the critical level leads to permanent oxidative stress in the cells. This could cause genomic instability and mutations, which are responsible for adaptation of cells to oxidative stress and their survival in an oxidative environment. In turn, these events could provoke malignancy. It is widely accepted that the balance between ROS and reducing equivalents in cells and tissues determines their redox status. The evaluation of tissue redox status has great diagnostic potential in cancer, as well as prognostic potential for cancer therapy, and could significantly contribute to the planning of appropriate treatment and to increasing the patients’ quality of life. The conventional therapeutic strategy is based on drugs that increase ROS generation and induce apoptosis in cancer cells. However, this therapeutic approach has serious disadvantages: the expression of various toxic side effects in normal (non-cancer) tissues. The current review describes the basics of free radical biology in carcinogenesis. The authors emphasize the different redox status of normal and cancer cells, which permits the use of this parameter as a new therapeutic target. The authors also outline some directions for the development of promising therapeutic strategies based on the regulation of redox signaling using combined therapy. The review is intended for a broad readership – from non-specialists to researchers in the field of cancer biochemistry and pharmacy (Adv Clin Exp Med 2013, 22, 6, 899–908).

Key words: cancer; reactive oxygen species, redox signaling, therapy.

Carcinogenesis is a multi-step process, accompanied by accumulated genetic alterations in the somatic cells. The targeted (initiated) cells in the primary cancer locus change their behavior. They are characterized by a selective growth advantage as a result of mutations in genes responsible for controlling cellular proliferation and death. These mutations include the up-regulation of proto-oncogenes and down-regulation of tumor suppressor genes [1, 2].

It is widely accepted that reactive oxygen species (ROS) are also among the main triggers and/or mediators of carcinogenesis. It is assumed that oxidative stress contributes to the initiation of cellular malignancy and the progression of cancer by causing a genomic instability [3–6].

The Chemical Nature and Major Endogenous Sources of ROS
ROS are generated as a result of one- or multi-electron reductions of oxygen. There are 2 types of ROS: 1) the free radical type – those that have
I or more unpaired electrons in their outer molecular orbitals (e.g., superoxide radical [O$_2^-$], nitric oxide radical [NO], hydroxyl radical [OH] and hydroperoxyl radical [HOO]); and 2) the non-radical type, which have unpaired electrons, but are highly reactive and can be converted to the radical type of ROS (e.g., hydrogen peroxide [H$_2$O$_2$], ozone [O$_3$], trioxidan [HOOOH] and nitric oxide [NO]).

ROS are generated either by exogenous sources such as pollutants, tobacco smoke, iron salts, radiation, etc., or by endogenous cellular sources. Cells produce ROS through multiple mechanisms. Major endogenous sources of ROS are 1) 4-electron reduction of oxygen in the mitochondria; 2) NADPH-dependent oxidases; 3) P-450-dependent monoxygenases; 4) xanthine oxidase; 5) lipoxygenases, cyclooxygenases, etc. Since mitochondria and NADPH-dependent oxidase complexes are the basic endogenous sources of ROS in carcinogenesis, the current article focuses mainly on these 2 factors (Fig. 1) [8, 9].

The mitochondrial electron-transport chain (ETC) consists of 4 multi-protein complexes (I–IV) embedded in the inner mitochondrial membrane. Complex I and complex II oxidize NADPH and FADH$_2$ respectively, and transfer the resulting electrons to ubiquinol, which carries the electrons to complex III. Complex III shunts the electrons across the intermembrane space to cytochrome $c$, which brings the electrons to complex IV. Complex IV then uses the electrons to reduce oxygen to water. Complexes I, II, and III generate superoxide radicals as a result of the electron flux through them. Complexes I and II generate ROS within the mitochondrial matrix, while complex III generates superoxide and releases it into either the intermembrane space or the mitochondrial matrix. The superoxide formed can subsequently be converted to other ROS, e.g. hydrogen peroxide. Hydrogen peroxide is a lipophilic substance and easily penetrates mitochondrial and plasmatic membranes, reaching the cytosol and extracellular environment. Thus, if there is mitochondrial dysfunction accompanied by excessive generation of superoxide and hydrogen peroxide, ROS can be found in the whole intracellular and extracellular space.

The other major endogenous source of ROS is the NADPH-oxidase pathway (Fig. 2) [10–12]. NADPH oxidases catalyze the reduction of oxygen with the production of superoxide, using NADPH as a reducing equivalent. The NADPH oxidase complex was initially found in phagocytes. NADPH oxidases are mainly expressed on the cell surface. The activation of NADPH oxidases occurs when the cytosolic components migrate to the cellular membrane. These enzymes generate superoxide at the plasmatic membrane and release it into the extracellular space, where it is converted

![Fig. 1. Generation of ROS in the mitochondria (according to West et al. [9]), SOD – superoxide-dismutase; GPx – glutathione peroxidase; CoQ – coen-zyme Q; Cyt c – cytochro-me c; VDAC – voltage dependent anion channel.](image-url)
into hydrogen peroxide. The extracellular hydrogen peroxide can subsequently penetrate through the plasmatic membrane into the cytosol. Recent studies suggest that NADPH-oxidase generation of superoxide can also occur in endosomes and the endoplasmic reticulum [13]. The superoxide generated in these intracellular compartments can be converted into hydrogen peroxide, which migrates into the cytosol and extracellular space.

Therefore, any dysfunction in the mitochondria and/or up-regulation and activation of the NADPH-oxidase complex can induce abnormal generation of ROS in somatic cells. Both events (mitochondrial dysfunction and up-regulation of the NADPH-oxidase complex) are observed in various cancers and they have a major impact on the planning of therapeutic strategies. This hypothesis will be discussed below.

**The Physiological Functions and Harmful Effects of ROS in Cells**

Low levels of ROS can activate cellular proliferation or survival signaling pathways via kinase activation and/or phosphatase inhibition, as well as via regulation of proteinases, including matrix metalloproteinases [14]. The most common mechanism of these regulatory processes is the interaction of ROS with cysteine residues, which results in the formation of disulfide bonds and the subsequent activation of signal transduction. In the context of carcinogenesis, it is important to note that ROS are considered to be regulators of the following major signaling mechanisms: extracellular signal-regulated kinases (ERKs), mitogen-activated protein kinases (MAPKs), phosphoinositide

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**Fig. 2.** Generation of ROS by the NADPH-oxidase complex (according to Chrissobolis & Faraci [12]), NOX – NADPH-oxidase
3-kinases (PI3Ks) and transcription factors such as hypoxia-inducible factors (HIFs). All of these intracellular components take part in cell proliferation, growth and survival [3, 6, 14, 15].

The dysregulation of the MAPK-signaling pathway can lead to uncontrolled proliferation or permanent cell cycle arrest [16]. These 2 processes are competitive and have opposite effects on cell survival. The level of ROS in cells and their environment is a very important regulatory factor, which is in direct cross-talk with MAPK activity and determines which of these 2 events will occur [6, 16, 17].

A similar relationship exists between the level of ROS and the ERK-signaling pathway, which is also involved in cell cycle arrest [3, 16, 17]. ERK-sustained activation of cyclin D1 expression is required throughout the G1 phase in order to proceed to the S phase of the cell cycle. Conversely, a high level of long-term ERK activation can provoke cell cycle arrest. It has been found that ROS inactivate the phosphatases responsible for the dephosphorylation of ERK and thus ensure sustained ERK activation [3, 16, 17].

The PI3K-signaling pathway is necessary for a number of cellular processes, including cell growth, survival, proliferation and mobility. This pathway can be affected by the redox status of the cell. The best known direct target in the PI3K pathway for oxidants is the tumor suppressor gene phosphatase and tensin homolog (PTEN). Hydrogen peroxide inactivates PTEN through the formation of a disulfide bond between the active site cysteine (Cys124) and a vicinal cysteine (Cys71) [3, 6, 18]. This process facilitates the subsequent activation of oncogenes.

High levels of ROS can directly induce oxidative damage in lipids, proteins and nucleic acids. ROS can participate in multistage carcinogenesis from initiation to malignant conversion, by causing oxidative DNA damage and mutations in proto-oncogenes and tumor suppressor genes, and subsequent activation of signal transduction pathways [1, 6, 14]. The p53 tumor suppressor gene and bcl-2 (B-cell lymphoma 2) proto-oncogene are the most extensively studied genes known to modulate cancer-related apoptosis [1, 6, 14].

At the initial stage of disease, cancer cells usually exhibit genetic instability and a significant increase in ROS level due to a “vicious circle” [6]. For example, ROS induce genetic mutations (especially in mitochondrial DNA), which subsequently lead to metabolic dysfunction and additional ROS generation. As a genomic guard, the p53 protein plays a major role in removing oxidative damage from nuclear DNA and mitochondrial DNA (mtDNA). P53 prevents oxidative genetic mutations and genomic instability. Moreover, p53 is also a transcription factor that regulates the expression of many pro-oxidant and antioxidant genes. The down-regulation and loss of p53 is associated with redox imbalance, increased production of ROS, mutagenesis and aggressive tumor growth. As Trachootham et al. wrote: “This is consistent with the high incidence of p53 mutation or loss of p53 function in over 50% of human cancer” [6], and especially in advanced and early stage of cancer [14, 19].

ROS induce almost all forms of DNA damage, including modifications of the nucleotide bases, strand breakage and DNA protein cross-links, but the specific spectrum of products depends on the type of ROS. ROS type-specific mutations are involved in the genesis of cancer. ROS may also play a key role in the development of cancer by inducing and maintaining oncogenic phenotypes of cancer cells [6, 14, 19]. Currently, oxidative stress is widely accepted as a major contributor to carcinogenesis.

Antioxidant Defense Systems and Carcinogenesis

The effects of ROS are balanced by antioxidant enzymes (e.g., superoxide dismutase [SOD], catalase, glutathione peroxidase, other peroxidases, etc.) and non-enzymic antioxidants (e.g., ascorbate, tocopherols, tocotrienols, carotenoids, natural flavonoids, melatonin, etc.) [7, 20].

Fig. 3 shows a schematic illustration of cellular redox homeostasis and the effects of ROS scavenging enzymes.

SOD is a class of enzymes that catalyze the dismutation of superoxide into hydrogen peroxide and oxygen. In humans, SOD exists in 3 isoforms: cytosolic Cu, Zn-SOD, mitochondrial Mn-SOD, and extracellular Cu, Zn-SOD [7]. It has been proved experimentally that a SOD defect is associated with several types of cancer, including hepatocellular carcinoma, colon cancer, breast cancer and laryngeal carcinoma. Diminished levels of SOD are detected in all patients with brain tumors in comparison with clinically healthy volunteers. For the past 20 years, Mn-SOD activity has been postulated to be low in all malignant tumors [21, 22]. Low levels of Mn-SOD have been observed in cancer cells using in vitro transformed cell lines, but other studies have shown variable expression of Mn-SOD in cancer [1, 21, 22]. Some types of cancer (e.g., breast cancer) are characterized by high levels of SOD and hydrogen peroxide. Therefore, the level of SOD is not indicative of carcinogenesis and cannot be used as a diagnostic marker or therapeutic target.
Catalase catalyzes the decomposition of hydrogen peroxide to water and oxygen [7]. Catalase has one of the highest turnover rates for all enzymes: one molecule of enzyme can convert approximately 6 m molecules of hydrogen peroxide to water and oxygen within a min [23]. The prognostic role of catalase in carcinogenesis is also disputable and currently it is not considered a valuable therapeutic target.

It is widely accepted that glutathione peroxidase is the major redox-modulating enzyme in mammals. Along with other peroxidases, peroxiredoxins, and thiol-reductases, glutathione peroxidase regulates the pool of reduced glutathione (GSH) – one of the major reducing equivalents in cells and body fluids [6, 7]. Many phospho-proteins and proteinases with GSH-containing cysteine residues undergo oxidation with the formation of disulfide bonds (GSSG), which is a trigger for the activation of signal transduction pathways. The oxidation of GSH to GSSG is a reversible process. The disulphide reductases (also known as redox proteins – thioredoxin [TRX] and glutaredoxin [GRX]) convert the disulphides to dithiols within the target protein and thus restore the reduced glutathione. An example of this redox-based signaling is the activation of apoptosis signal-regulating kinase 1 (ASK1). ASK1 is bound to a reduced TRX in its inactive form. ROS oxidize TRX, causing its disassociation from ASK1, which allows the auto-phosphorylation of ASK1 and its activation [3, 24].

Various types of cancers are characterized by different expression of antioxidant enzymes, as well as by different levels of non-enzymatic antioxidants. It is important to note that the total antioxidant capacity has to be considered in cancer diagnostics and therapy.

**ROS/Antioxidant Balance in Normal Cells and in Cancer Cells – Redox Status as a Diagnostic Marker and Therapeutic Target**

Summarizing, over 50 years of experience in free radical biology and medicine indicates that redox signalling has a crucial role in carcinogenesis, as noted in the current authors’ earlier publications [25–27], as well as by other authors [2–6, 14].
The cells and tissues of healthy mammals are characterized by a low steady-state level of ROS and some constant level of reducing equivalents, while cancer cells are characterized by increased levels of ROS and reducing equivalents (Fig. 4) [25]. Cancer cells are also characterized by abnormal production of reducing equivalents (e.g., NADPH, NADH) as a result of accelerated glycolysis (the Warburg effect) and pentose phosphate cycle. However, these reducers are rapidly consumed to maintain accelerated anabolism, which is necessary for cell proliferation and immortalization.

As Barrera wrote: “A moderate increase in ROS can promote cell proliferation and differentiation” [28]. However, extremely excessive amounts of ROS can cause irreversible oxidative damage to biomacromolecules, apoptosis and cell death [6]. Therefore, maintaining ROS homeostasis at low levels is crucial for normal cell survival, while a moderate enhancement of ROS is associated with abnormal cancer cell growth and disruption of redox homeostasis [6].

Prolonged operation of cells at abnormal steady-state levels of ROS provokes genetic mutations, which makes them well adapted to oxidative stress. This process is at the basis of malignant transformation. Cancer cells are usually characterized by increased antioxidant capacity, as noted in the authors’ earlier publication [20]. Cells that survive intrinsic oxidative stress mobilize a set of adaptive mechanisms, which not only activate ROS-scavenging systems to cope with the oxidative stress, but also inhibit apoptosis. As De Luca et al. wrote: “Such adaptation contributes to malignant transformation, metastasis and resistance to anticancer drugs” [29].

Harris et al. reported that normal epithelial cells, exposed to low but continuous levels of exogenous oxidants, become resistant to subsequent oxidative stress even at a higher level [30]. This observation suggests that cells can adapt to survive under certain levels of oxidative stress. As Barrera wrote: “Those cells that survive oxidative stress are likely to have acquired adaptive mechanisms to counteract the potential toxic effects of elevated ROS and to promote cell-survival pathways” [28]. For example, Nonn et al. reported that HR as oncogene-transformed cells, which exhibit increased superoxide and hydrogen peroxide levels, are also characterized by increased levels of antioxidants (e.g., peroxiredoxin-3 and thioredoxin peroxidase) in comparison with their non-cancer parental cells [31]. It seems likely that their enhanced antioxidant capability serves as a compensatory mechanism to evade ROS-induced apoptosis. Thus, the abrogation of this adaptation mechanism could be an attractive strategy to preferentially affect cancer cells and may have promising therapeutic implications [6].

The authors’ recently published data on experimental animals showed that reduction exceeds oxidation in the tissues of healthy organisms, while oxidation exceeds reduction in the tissues (both cancer tissues and non-cancer tissues) of cancer-bearing organisms [25–27]. Moreover, the tissue redox status is very sensitive to cancer progression.

Fig. 4. The balance between reactive oxygen species (ROS) and reducing equivalents (RE) in normal and cancer cells (according to Zhelev et al. [25])
and anti-cancer therapy [27]. These data suggest that tissue redox status could be a diagnostic marker, a therapeutic target, and a hallmark for evaluation and for planning the therapeutic strategy.

**Therapeutic Strategies in Cancer Based on Redox Signaling**

The targeting of unique biochemical alteration in cancer cells might be a feasible approach to achieving therapeutic activity and selectivity and perhaps to prevent the development of drug resistance [6].

As Beck et al. wrote: "Agents such as arsenic trioxide, which impair the function of the mitochondrial respiratory chain, are known to increase the production of superoxide" [32]. Radical intermediates are also formed by compounds known as "redox cyclers", which may react with flavoprotein reductases such as cytochrome P450-reductase and NAD (P) H-dependent quinone oxidoreductase (NQO1). Motexafin (an inhibitor of thioredoxin reductase and ribonucleotide reductase) and anthracyclines (e.g., daunorubicin and doxorubicin – broad antibiotics used in conventional cancer chemotherapy) are good examples of redox cyclers [6, 33, 34]. Anthracyclines are redox-active because of their quinine-hydroquinone structure. They are widely used to treat various malignant tumors, but their clinical efficacy and use are often limited by side effects due to elevated ROS production in non-cancer tissues. These anticancer drugs are well-known generators of superoxide. The side effects of doxorubicin may also be due to intracellular chelation of iron, which may trigger a Fenton-type reaction and subsequent generation of highly reactive hydroxyl radicals [6, 33, 34].

Bleomycin and pharmorubicin are anticancer antibiotics that are most effective for treatment of lymphomas, certain types of squamous-cell carcinomas and testicular carcinomas. Their side effects constitute one of the major obstacles to the use of these antibiotics as anticancer drugs: Pharmorubicin is cardiotoxic and bleomycin induces pulmonary toxicity as a result of increased generation of ROS not only in cancer cells, but also in non-cancer cells and tissues [35].

Therapeutic selectivity is essential in cancer treatment. Some compounds exhibit a potent ability to promote ROS generation predominantly in cancer cells and show promising anticancer activity in vitro and in vivo [6].

As Shaaban et al.: "To maximally exploit the ROS-mediated cell-death mechanism as a therapeutic strategy, it is possible to use a combination of drugs" [36]. For example: 1) a drug that induces ROS generation in cancer cells, but not in normal cells; and 2) a drug that suppresses antioxidant capacity in cancer cells, but not in normal cells. Zhou et al. reported that a combination of the ROS-generating agent arsenic trioxide and SOD-inhibitor 2-methoxyestradiol (2-ME) shows potent activity against primary chronic lymphocytic leukemia (CLL) and significantly increases the cytotoxicity of 2-ME in CLL cells that were resistant to 2-ME alone [37]. It has also been established that a combination of arsenic trioxide and GSH depletion, mediated by ascorbic acid, is effective in the treatment of multiple myeloma [38, 39].

Beta-phenylethyl isothiocyanate (PEITC) is a natural compound known to increase intracellular ROS levels, preferentially killing ovarian epithelial cells, but not normal cells; injections of PEITC in mice grafted with Ras-transformed ovarian epithelial cells prolonged their survival [3] This suggests that modulating ROS levels is a promising potential therapeutic strategy in cancer. These findings have been confirmed by the observation that mice grafted with an ovarian cancer cell line expressing a high Akt activity showed a reduction in tumor size after treatment with rapamycin and PEITC [3]. Rapamycin analogs are currently in use in clinical trials.

The presence of stable nitroxyl radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) in antitumor compounds such as 1-(2-chloromethyl)-3-cyclohexyl-1-nitrosourea (CCNU) reduces their toxicity and increases radio-sensitizing properties, imparting a beneficial influence on the antineoplastic properties of this drug. Nitroxide-labeled analogs of CCNU showed lower toxicity and higher anticancer activity in experimental tumor models [35]. It has been reported that nitroxide-labeled nitrosourea increases the cytotoxic effect of bleomycin and pharmorubicin in human hematological neoplasms, but not in normal lymphocytes [35]. Nitroxide labeling could also decrease the toxic side effects of these antibiotics by scavenging superoxide. Thus, the combination of bleomycin (at lower doses) with nitroxide-labeled nitrosourea would decrease bleomycin-induced pulmonary toxicity [35]. Several ROS-generating chemical substances are currently undergoing clinical trials as a part of a combined anti-cancer therapy.

Obviously, significantly increasing ROS is a good strategy for killing cancer cells. However, the generation of ROS has to be localized predominately in the cancer area to avoid side effects on non-cancer cells and tissues. In this context, carbon ion radiotherapy (CIRT) is unique and very
promising. As Kamada wrote: “CIRT is well-localized and superior-depth dose distribution of irradiation and the concomitant local generation of ROS in addition to less repairable radiobiological effects in the cancer area. Since 1994, when the 1st clinical study of cancer therapy with carbon ion beams was started, about 50 clinical studies have been completed safely and effectively. These studies revealed that intractable cancers such as inoperable bone and soft-tissue sarcomas can be cured safely in a shorter overall treatment time, as can cancers in the head, neck, lung, liver, prostate, and postoperative pelvic recurrence of rectal cancer. The number of patients receiving CIRT has reached 6,000, and this anti-cancer therapy was approved as a highly advanced medical technology in 2003. Based on these experiences, a new-generation beam delivery facilities such as a 3D scanning method with a pencil beam was developed and put into operation since May 2011” [40].

Currently there are serious limitations to the widespread application of CIRT because of the need for specific apparatus (e.g., heavy ion medical accelerators) and the high costs. Until CIRT becomes a conventional therapeutic technology, efforts are focused on improving existing, widely used ROS-modulated anti-cancer strategies such as conventional cytostatic chemotherapy and/or radiotherapy using X-rays. The ROS generated by anticancer agents and radiotherapy are effective in killing cancer cells, but they can alter other cellular pathways and to provoke various side effects in non-cancer cells and tissues. The most serious side-effects observed in chemotherapy and radiotherapy, are nephrotoxicity, cardiotoxicity and ototoxicity [41].

The development of oxidative stress in the non-cancer tissues of a cancer-bearing organism is a serious problem for both chemotherapy and radiotherapy. Combining radiotherapy and/or standard chemotherapy with antioxidants that increase the protection of non-cancer tissues against oxidative stress should be explored as a therapeutic strategy [6]. However, it would conflict with ROS-mediated apoptosis and necrosis in cancer cells. As Maiti et al. wrote: “The clinical benefit of using antioxidant supplements along with chemotherapy and radiotherapy is highly debatable, and not conclusive. Some of the clinical studies suggest that the antioxidant supplemented group had a worst survival rate, than the group who did not use antioxidant supplements. Although in some cases, use of antioxidant has fewer side effects leading to less damage to normal tissues, but with a decrease in the overall survival rate. However, it is also believed that antioxidant supplemented reduction of side-effects depends mainly on using specific anticancer drugs for certain cancers” [41].

The reports of other groups also support this assertion [42, 43].

It is important to note that persistent ROS generation as a result of chemo- and/or radiotherapy can also activate the antioxidant adaptive response system and thus increase the resistance of cancer cells, which will negatively affect therapeutic outcomes [44]. For example, radiotherapy leads directly to the ionization of water, then to the generation of ROS, which are amplified by mitochondria, generating even larger quantities of ROS. Irradiation-induced ROS activate several proliferative and anti-apoptosis pathways (e.g., the MAPK pathway, the release of VEGF, the increase of survivin, etc.), resulting in cytoprotection [44–47]. Therefore, as Dimauro et al. wrote: “Antioxidant adaptive response system, activated by radiation, may be highly relevant to tumor response during standard clinical dose-fractionated radiation therapy” [44].

As Trachootham et al.: “The role of oxidative stress in promoting cancer development and causing oxidative damage provides different rationales for two opposite therapeutic strategies against cancer” [6]. The 1st approach is to increase ROS-scavenging capacity using antioxidants, thereby abrogating ROS signaling and suppressing tumor growth, as well as avoiding side effects on normal cells and tissues. However, several antioxidants used in clinical trials were associated with increased cancer incidence. This adverse effect of antioxidants might be related to the activation of the adaptive response system and the inhibition of ROS-mediated apoptosis in cancer cells. A 2nd, opposite approach is to treat cancer cells with pharmaceuticals possessing strong pro-oxidant properties, which will abrogate the cellular antioxidant systems of cancer and increase ROS generation above the threshold level, with the subsequent induction of apoptosis and cell death. However, the chemotherapeutic agents and radiotherapy that accelerate ROS generation in cancer cells have many side effects on normal tissues. Since both of these 2 strategies have disadvantages, combined therapy seems to be a promising option. It is necessary to look for a combination of substances expressing therapeutic synergy as a result of differentiated effects on cancer and normal cells: substances with increased ROS-scavenging properties targeting normal cells and substances with increased ROS-generating properties targeting cancer cells. Such a combination could decrease the toxic side effects of anticancer drugs in normal cells and preferentially attack cancer cells through site-specific increases of the ROS in them and the induction of apoptosis and necrosis in the cancer locus. This combined approach is a subject that calls for investigation.
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Conflict of interest: None declared

Received: 7.04.2013
Revised: 22.05.2013
Accepted: 26.11.2013