Drug Discovery Today • Volume 00, Number 00 • January 2018 PERSPECTIVE

ELSEVIER

feature

# Administration of antioxidants in cancer: debate of the decade

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**Several randomized clinical trials have divulged that administration of antioxidants during chemotherapy decreases the effectiveness of treatment. Hence, the characteristic feature of this article is extensive assessment of putative benefits and potential risks of natural and synthetic antioxidant supplementation, administered with chemotherapy, based upon the available preclinical and clinical data. After analyzing mixed results, it was concluded that current FDA guidelines should be followed before supplementing antioxidants during cytotoxic treatment. Nevertheless, contradictory experimental animal models opposing human clinical trials discourage the concurrent administration of antioxidants ostensibly owing to the possibility of tumor protection and reduced survival.**



## Reactive oxygen species (ROS) in cancer

Cancer, a proliferative syndrome, is the leading cause of death worldwide. Recent evidence reports that cancer cells persistently exhibit high ROS levels, as a consequence of metabolic, genetic and microenvironment-associated alterations. ROS are generated, primarily in mammalian cells from the metabolism of oxygen at molecular levels, as a part of mitochondrial aerobic respiration. High proportions of ROS, being intoxicating, can readily damage or mutate the DNA of cells by escaping from the respiratory chain [1]. Thus, to antagonize their effects and to restore redox balance, cells are programmed to retune their homeostatic parameters [2]. Tissue damage owing to ROS is caused by reacting with lipids in cellular membranes, sulfhydryl groups in DNA and cross-linking or fragmentation of ribonucleoproteins [3]. Figure 1 depicts the ROS-mediated tumorigenesis and its ostensible mechanistic pathways. The role of antioxidants in combating the ROS-triggered damage in tumor cells has been implicated in chemoresistance with pitiable prognoses. Here, we unravel the potential use of antioxidants together with chemotherapeutic agents [1].

## Antioxidants

Antioxidants are the agents that have the ability to prevent, retard or eradicate oxidative stress of a molecule [4]. Antioxidants are organic or inorganic compounds, either abundant naturally or synthesized industrially. When added to a formulation even in minuscule quantities, they tend to give up their electron(s) to the free radicals, subsequently neutralizing them, preventing the cells from potential damage and curing numerous diseases [5]. The efficacy of exogenous antioxidant compounds, to safeguard the tissues from oxidative stress, is dependent upon the nature of the antioxidant, its physicochemical and biopharmaceutical properties, and accessibility at the target site [6]. Antioxidants are also useful as dietary supplements for sustaining health, disease prophylaxis or for reducing the adverse effects of chemo- and radio-therapy [7].

### *Existing natural and synthetic antioxidants*

Antioxidants can be classified on the basis of their origin, solubility (i.e., aqueous or lipid) and mechanism of action (i.e., metal chelation or blocking the chain reaction) [8]. On the basis of their origin, antioxidants can be categorically described as natural or synthetic.

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https://doi.org/10.1016/j.drudis.2018.01.021

Please cite this article in press as: Khurana, R.K. et al. Administration of antioxidants in cancer: debate of the decade, Drug Discov Today (2018), https://doi.org/10.1016/j.drudis.2018.01.021

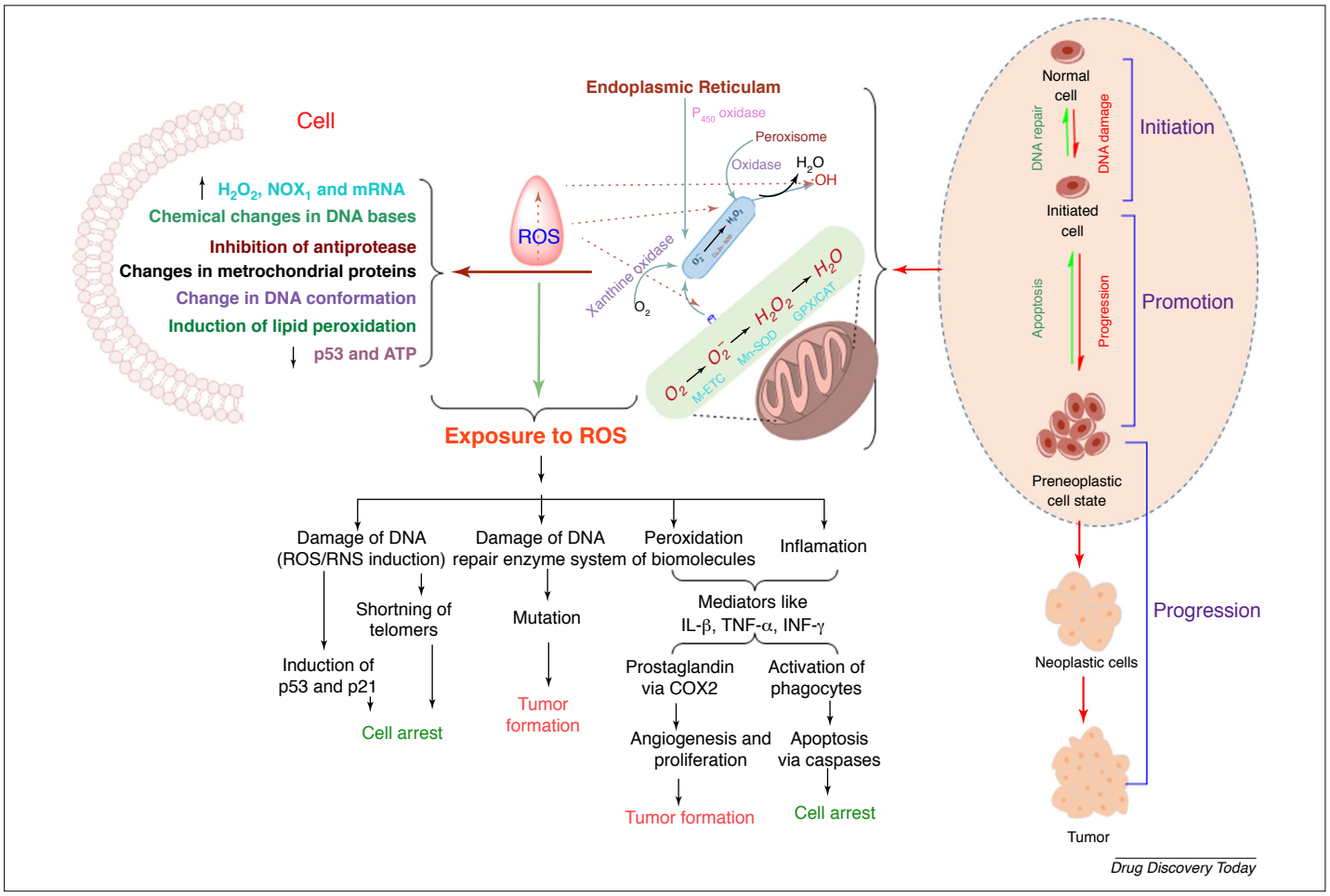


**FIGURE 1**

ROS-triggered processes for tumor formation and cell damage. Abbreviations: ATP, adenosine triphosphate; DNA, deoxyribonucleic acid; $NOX_1$, NADPH oxidase 1; mRNA, messenger ribonucleic acid; E-ETC, mitochondrial electron transfer chain; Mn-SOD, manganese-dependent superoxide dismutase; GPX, glutathione peroxidase; CAT, catalase; p21, cyclin-dependent kinase inhibitor p21; p53, cellular tumor antigen p53; $P_{450}$, cytochrome $P_{450}$ enzymes; ROS, reactive oxygen species; RNS, reactive nitrogen species; IL-β, interleukin beta; TNF-α, tumor necrosis factor alpha; INF-γ, interferon gamma; COX2, cyclooxygenase 2.



### *Natural*

Antioxidants from natural origins include flavonoids, carotenoids and carnosine, enzymes, vitamins, chelators, as well as other phenolic and polyphenolic compounds. Antineoplastic activities of lycopene [9], resveratrol [10], ascorbic acid, α-tocopherol [11], capsaicin [12], curcumin [13], garlic [14] and quercetin [15] have been well documented. However, the mechanistic pathway(s), by virtue of antioxidant molecules that scavenge the free radicals, prevent rancidity and control autooxidation of foodstuffs, can vary [16]. Recent findings have demonstrated the antibacterial, anti-inflammatory, anticancer and antimutagenic effects of various natural antioxidants in cells.

### *Synthetic*

Besides natural resources, antioxidants can be produced synthetically too. Several food and pharmaceutical products currently available comprise synthetic antioxidants to improve the shelf-life of therapeutic agents that are susceptible to chemical degradation by oxidation. As foodstuffs, synthetic antioxidants can inhibit some ROS-associated cell injuries in conditions of elevated oxidative stress. Synthetic antioxidants such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA) and 6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline (ethoxyquin) protected against the formation of dimethylbenz[a]anthracene (DMBA)-initiated mammary tumors [17]. However, preclinical and clinical reports suggest that synthetic antioxidants cannot afford appropriate protection against oxidative stress [18].

### *How safe are natural antioxidants?*

Epidemic studies suggest that a diet rich in antioxidants like flavonoids, carotenoids, tocopherols, vitamin C, polysaccharides and amino acids, and their derivatives, protects against various harmful degenerative ailments. Intake of phenolic compounds in the food has been accepted in the past owing to absence of toxicity [19]. Besides the active components, natural antioxidants comprise several other substances exhibiting their synergistic potential. Despite the numerous health benefits and wide applicability of natural antioxidants, the safety profile of these allied substances has not been completely ascertained [20].

## Antioxidant-derived benefits in cancer: positive and negative preclinical and clinical reports

Various studies have been conducted to employ dietary antioxidant supplements in cancer patients. Surprisingly, mixed reports have been filed by the researchers on the concomitant use of anticancer drugs and antioxidants. Table 1 presents a bird's eye view account on preclinical and clinical studies indicating an overview of


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**TABLE 1**

**Preclinical and clinical studies depicting the efficacy of the antioxidants in various cancers**

**Preclinical studies**

| Type of cancer | Chemotherapeutic agent(s) | Antioxidant(s) | Delivery system | Animal model/ cell line | Significant outcomes | Effectiveness of co-therapy | Refs |
|---|---|---|---|---|---|---|---|
| Breast cancer | TMX | QCT | SNEDDS | Female SD rats | QCT along with TMX via SNEDDS improved the therapeutic response of TMX | Effective | [15] |
| Breast cancer | MTX | β-CRT | Functionalized lipid–polymeric-hybrid nanoparticles | Female albino wistar rats | Residual tumor progression was very low (~32%). β-CRT also ameliorated the MTX-induced toxicity | Effective | [28] |
| Breast cancer | DOX | CoQ10 | CoQ10-loaded nanoparticles and Dox-loaded nanoparticles | Female SD rats | In MCF-7 cells, *in vitro* cell cytotoxicity study demonstrated initial antagonism up to 48 h, when compared with other treatments. CoQ10-NPs and Dox-NPs showed ~1.7-fold and 4.0-fold increased antitumor efficacy, respectively | Effective | [24] |
| Breast cancer | DOX | CoQ10 | Liquid crystalline nanoparticles | Female SD rats | Synergistic action at 1:10 (Dox to CoQ10) dose ratio | Effective | [29] |
| Skin cancer | SA | QCT | Nanomixed micelles | Female Balb/c mice | Improved antineoplastic action caused by combined strategy | Effective | [30] |
| Breast cancer | TMX | NG | SNEDDS | Female wistar rats | Efficacy was improved in synergistic way by reducing tumor volume and increased survival rate of the animals | Effective | [31] |
| Human adenocarcinoma cell | MTX | LYC | SLNs of LYC co-administered with MTX | MCF-7 cell lines | Mortality in MCF-7 cells was significantly increased compared with MTX alone | Effective | [9] |

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**Clinical studies**

| Type of cancer | Chemotherapeutic agent(s) | Antioxidant(s) | Drug–antioxidant treatment regimen | Subject particulars | Significant outcomes | Effectiveness of co-therapy | Refs |
|---|---|---|---|---|---|---|---|
| Small-cell lung cancer | Standard small-cell lung cancer treatment | Vitamins, trace elements and fatty acids | – | 18 non-randomized patients (14 men and 4 women, 60.4 ±7.8 years of age) | Mean survival time was 505 days. 77% of the patients survived for >1 year, 33% >2 years, 5% survived >5 years. At the end of the study, 44% were alive for 32 months | Effective | [32] |
| Metastatic colorectal cancer | Irinotecan | MLT | Irinotecan: 125 mg/m$^2$ per week i.v., MLT: 20 mg orally in the evening | 30 patients; 14 received irinotecan + MLT and 16 received irinotecan alone | MLT group had significant disease control. Although toxicities were reduced by MLT, yet was not statistically significant | Effective | [33] |
| Advanced non-small-cell lung cancer (NSCLC) (Stages IIIb and IV) | PTX | Ascorbic acid, vitamin E and β-CRT | PTX (225 mg/m$^2$) + carboplatin Ascorbic acid (6100 mg/day), vitamin E (1050 mg/day) and β-CRT (60 mg/day) | 136 patients; 64 received chemotherapy + mixed antioxidants, 72 received chemotherapy alone | Antioxidant had insignificant effect upon chemotherapy treatment, and did not reduce toxicities | Challenged | [11] |
| Combined lung and ovarian cancer | CPT, cyclophosphamide, etoposide | DDTC | CPT (100 mg/m$^2$) and cyclophosphamide (in ovarian cancer) or etoposide (in lung cancer) | 195 patients | DDTC did not demonstrate any significant chemoprotective effect against CPT-induced toxicities. In fact, DDTC-treated patients showed more nephrotoxicity | Challenged | [34] |
| Various malignant tumors | CPT | Vitamin C, vitamin E and selenium | CPT: 100 mg/m$^2$ per cycle. Antioxidants: 1000 mg vitamin C (as l-ascorbic acid), 400 mg vitamin E (as dl α-tocopherol-acetate) and 100 μg selenium (as sodium selenite) were dissolved in beverages | 48 patients; 25 received CPT + mixed antioxidants. 23 received CPT alone | Patients did not show any sign of reduced nephrotoxicity, ototoxicity or bone marrow toxicity, upon co-administration of antioxidants. Patient compliance to antioxidant supplementation beverage was poor, with 46% throughout the whole study period | Challenged | [35] |
| Advanced ovarian cancer | CPT | GSH | CPT: 40 mg/m$^2$. GSH: 1500 mg/m$^2$ i.v., 15 min prior to chemotherapy | 24 patients | GSH failed to reduce toxicities, because there was no significant difference between antioxidant and control groups | Challenged | [36] |

Abbreviations: β-CRT, β-carotene; CPT, cisplatin; DDTC, diethyldithiocarbamate; DOX, doxorubicin; CoQ10, coenzyme Q10; GSH, glutathione; LYC, lycopene; MLT, melatonin; MTX, methotrexate; NG, naringenin; PTX, paclitaxel; TMX, tamoxifen; QCT, quercetin; SA, salicylic acid; SNEDDS, self-nano-emulsifying drug delivery system; SLNs, solid lipid nanoparticles.





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effectual or not so effectual relationship(s) of antioxidant(s) with chemotherapeutic agent(s) and/or radiation, while being used to treat cancer simultaneously.

In a nutshell, the results of these studies are somewhat contradictory. It was obvious from the studies that the antioxidants, when administered along with other chemotherapeutic agents, were effective in animals. However, the efficacy was challenged when the results were attempted to be reproduced in humans. Accordingly, despite active research, investigating proper supplementation of antioxidants and other bioactives is still not certain to make a definite proclamation regarding their usage during conventional chemotherapy or radiotherapy. Table 2 summarizes the various trials conducted on antioxidants.

### *Are natural antioxidants better and safer than synthetic antioxidants?*

Besides therapeutic agents, natural antioxidants have demonstrated their promise to prevent and treat various diseases owing to their wide chemical diversity, multi-targeting actions and good safety profiles. Some natural antioxidants are even in clinical trials, whereas others have been permitted for human use. Although natural antioxidants are usually composed of numerous bioactives in different amounts and proportions, it is usually difficult to calculate their safe concentrations, because no such safety tests are reported. With synthetic antioxidants, by contrast, it is easier to earmark which antioxidants are safer, owing to the availability of requisite safety tests [21].

**TABLE 2**

**Selected human trials conducted on antioxidants**

| Trial | Antioxidant(s) | Observation(s) | Refs |
|---|---|---|---|
| Linxian General Population Nutrition Intervention | 15 mg β-CRT, 30 mg α-TCP and 50 μg selenium daily for 5 years | • People who took antioxidant supplements had a lower risk of death from gastric cancer, but not from esophageal cancer<br>• Risk of developing gastric and/or esophageal cancer was not affected by antioxidant supplementation<br>• Results from this trial, 10 years after antioxidant supplementation ended, did not indicate any reduced risk of deaths from gastric cancer for those who took antioxidant supplements compared with those who did not | [37] |
| α-TCP/β-Cancer Prevention | α-TCP (50 mg/day) and/or β-supplements (20 mg/day); for 5 to 8 years | • Showed higher incidence of lung cancer among the volunteers who took β-supplements, but no effect was seen with α-TCP supplementation<br>• Hardly any effect of β- or α-TCP supplementation was observed on the incidence of other cancers | [38] |
| Carotene and Retinol Efficacy Trial | Daily supplementation for 12 years with 15 mg β- and 25 000 IU retino (vitamin A) | • Increased lung cancer and deaths from all other causes<br>• Adverse effects persisted up to 6 years after supplementation ended, although an insignificant increase in lung cancer and all-cause mortality was observed<br>• Also, β-CRT and retinol supplementation exhibited no effect on the incidence of prostate cancer | [39] |
| Physicians' Health Study I | Long-term β-CRT supplementation (50 mg every other day for 12 years) | • β-CRT supplementation showed no effect on any of the outcomes in smokers or nonsmokers | [40] |
| Supplémentation en Vitamines et Minéraux Antioxidants | Daily supplementation with vitamin C (120 mg), vitamin E (30 mg), β-CRT (6 mg) and minerals, selenium (100 μg) and zinc (20 mg), for a median of 7.5 years on incidence of cancer and cardiovascular disease in French men and women | • Showed no effect on the incidence of cancer or cardiovascular disease<br>• Lower incidence of cancer and all-cause mortality among men, and an increase in skin cancer incidence, including melanoma among women, was observed<br>• Beneficial effects of the supplements for men disappeared within 5 years of ending supplementation, as did the increased risk of skin cancer among women | [41] |
| Heart Outcomes Prevention Evaluation – The Ongoing Outcomes | α-TCP supplementation (400 IU) for a median of 7 years on cancer incidence, death from cancer and the incidence of major cardiovascular events | • No effect was observed on cancer incidence, deaths from cancer or incidence of major cardiovascular events | [42] |
| Selenium and Vitamin E Cancer Prevention Trial | Daily supplementation with selenium (200 μg), vitamin E (400 IU) or both for reduced incidence of prostate cancer in men aged 50 years or more | • Use of these supplements for a median duration of 5.5 years did not reduce the incidence of prostate or other cancers<br>• After an average 7 years, i.e., 5.5 years on supplements and 1.5 years off supplements, there were 17% more cases of prostate cancer among men taking vitamin E alone than among men taking placebo<br>• No increase in prostate risk was observed for men assigned to take selenium alone or vitamin E plus selenium, compared with men assigned to take placebo | [43] |
| Physicians' Health Study II | Supplementation with 400 IU vitamin E every other day, 500 mg vitamin C every day or a combination of the two would reduce the incidence of cancer in male US physicians aged 50 years or more | • Use of these supplements for a median of 7.6 years did not reduce the incidence of prostate cancer or other cancers, including lymphoma, leukemia, melanoma and cancers of the lung, bladder, pancreas, colon and rectum | [44] |

Abbreviations: β-CRT, β-carotene; α-TCP, α-tocopherol.





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Moreover, the usage of carotenes, phospholipids, tocopherols, ascorbic acid and its esters is strongly endorsed because of their generally recognized as safe (GRAS) status, relative inexpensiveness and easier availability [20]. Scientific data on antioxidants in relation to cancer have been generated from human, epidemiological and *in vitro* and *in vivo* experimental studies (Table 3). Herein, outcomes of vital preclinical and clinical studies are summarized to dedicate a relationship of antioxidant(s) and chemotherapeutic agent(s)

**TABLE 3**

**Preclinical and clinical evidence of antioxidants**

**Preclinical evidence**

| Treatment | Experimental model | Results | Refs |
|---|---|---|---|
| Curcumin + radiotherapy | SCC1, SCC-9, A431 and KB of head and neck squamous cell carcinoma | Increased antitumor effect of radiation | [45] |
| EGCG + radiotherapy | Tumor cervical cells (HeLa), multiple myeloma (IM-9) and leukemic (K-562) | Decreased cell proliferation; increase apoptosis and necrosis | [46] |
| Melatonin + radiotherapy | CD2-F1 mice | Increased survival of animals | [47] |
| *N*-acetylcysteine + doxorubicin | Model of heart failure in Japanese white rabbits | Decreased apoptosis in cardiomyocytes | [48] |
| Vitamin C + doxorubicin | Cell lines of chronic myelogenous leukemia (K562) and lymphoma (RL) | Increased resistance to treatment | [49] |
| | Mice with RL cell xenografts | Larger tumors in mice | |
| Suppression of peroxiredoxin + doxorubicin | MCF-7 human breast tumor cells | Increased apoptotic effect of drug | [50] |
| EGCG + doxorubicin | Colorectal tumor cells (BEL-7404/DOX) | Increased cell death and sensitivity to drug | [51] |
| Resveratrol + paclitaxel | Human breast tumor cells | Decreased antitumor action of drug | [52] |
| Nitroxide + docetaxel or doxorubicin | Mice with breast tumor cells xenografts | Decreased side effects without interfering with treatment efficacy | [53] |
| Quercetin at low doses + cisplatin, 5-FU, taxol or pirarubicin | Athymic nude mice with ovarian tumor cells (C13*) xenografts | Decreased efficiency of the treatment | [54] |
| High dose of vitamins A, E and selenium + cisplatin | Tumor cells of colon (COLO-205-GFP) induced in mice | Significantly lower growth of tumors | [55] |
| Curcumin + cisplatin | Liver tumor cells (HA22T/VGH) | Increased cytotoxic effect of drug | [56] |
| | HNSCC tumor cells (CAL27, UMSCC) | | [57] |
| *N*-acetylcysteine before or up to 1 h after the drug + cisplatin | Human ovarian carcinoma cells (SKOV3), human SCLC tumor cells (B.5 LX-1), human glioblastoma cells (U87) and rat fibroblasts | Blockade of proapoptotic effect of drug | [58] |
| *N*-acetylcysteine up to 4 h after drug + cisplatin | Long-Evans rats | Otoprotection along with efficient treatment | [59] |
| Lycopene + cisplatin | Adult male SD rats | Decreased renal toxicity with sustained efficacy of treatment | [60] |

**Clinical evidence**

| Treatment | Disease | Results | Refs |
|---|---|---|---|
| High dose of vitamins C and E + radiotherapy | Head and neck cancer | Improved adverse effects, decrease effectiveness of the treatment | [61] |
| Normal dose of vitamins C and E, and β- + cisplatin + radiation | Cervical cancer | Reduced oxidative damage, enhanced muscle strength and lower fatigue | [61] |
| EGCG + radiotherapy | Breast cancer | Levels of angiogenic factors and HGF lowered down | [62] |
| Uncaria tomentosa + radiation | Breast cancer | Decreased the adverse effects with least interference with the treatment efficiency | [62] |
| *N*-acetylcysteine and vitamin E + vincristine, doxorubicin, cytosine arabinoside, cyclophosphamide and 6-mercaptopurine + radiation | Acute lymphoblastic leukemia | Lowered incidence of toxic hepatitis, decreased the need of blood and platelet transfusions during treatment | [63] |
| Melatonin + cisplatin + etoposide or cisplatin + gemcitabine | Advanced solid neoplasms | Higher rate of tumor regression, greater two-year survival rate | [64] |
| Melatonin + oxaliplatin and 5-FU | Gastrointestinal cancer | | |
| Melatonin in combination with chemotherapy | Advanced non-small-cell lung cancer | Decreased side effects with no better rates of survival | [65] |

Abbreviations: EGCG, epigallocatechin gallate; 5-FU, 5-fluorouracil; HGF, hepatocyte growth factor.



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and/or radiation therapy, while being used to treat cancer.

## Recommendations regarding administration of antioxidants

Recently, in 2016, the FDA published the latest Nutrition Facts Label for packaged foods based on scientific facts including the link between diet and chronic diseases, such as obesity and heart disease, and ordered that the consumers should be better informed of food choices [22]. Coming up with newer regulatory guidance, the FDA tends to dissuade the over-usage of antioxidants, and discourages the false label claims made for various food commodities and dietary supplements. The only antioxidants listed in the FDA sheets are vitamin C, vitamin E and β-carotene [23].

A study conducted on the usage of antioxidants during ongoing chemotherapy suggested that 18% of the subjects, despite consuming α-tocopherol and β-carotene as antioxidant supplements, developed lung cancer unexpectedly, thus discouraging simultaneous administration of antioxidants with the chemotherapeutic agents [24]. Hence, the FDA proposed that an antioxidant claim can only be made for nutrients with a recommended daily intake (RDI) as stated in the compendium, such as for ascorbic acid or vitamin E. However, no such claim can be made for other phytochemicals such as quercetin, elagic acid and caffeic acid.

## Future trends: impact of nanotechnology on potential of antioxidants in cancer therapeutics

The pharmacological treatments employing antioxidants can result in diminished cancer-associated deaths. The nanoconstructs of several antioxidants, approved by the FDA, are currently in active preclinical and clinical trial phases against cancer. Although various associated challenges (such as poor bioavailability owing to poor aqueous solubility, low permeability and short self-life) obstruct the translation of antioxidant therapies against cancer, the research is still in progress. Nanochemoprevention is a readily available tool to prevent and manage cancer by attaining higher concentrations of antioxidants to reach the specific target site. A great deal of research is still underway to understand the long-term hazards of nanotechnology-derived antioxidant products. Nevertheless, with the upcoming advances in the domain of nanotechnology, coupled with progressive applications of nanoparticles in cancer, one can anticipate enormous success for nanotechnology-driven rational use of antioxidants to combat this dreadful disorder in the near future.

## Concluding remarks

With the expanding choice of agents mediating their activity through ROS, antioxidants have lately entered into the clinical setting. Biochemical activity of antioxidants has established its preventive measures against cancer through several cellular processes, including apoptosis [25]. However, the scarcity of randomized and well-designed controlled clinical trials has led to limited exploration of the outcomes of concurrent usage of antioxidants with other chemotherapeutic agents. Haplessly, however, several early studies on antioxidants were poorly designed, thus providing inconsistent outcomes [26]. Moreover, in light of reported preclinical and clinical evidence, mixed outcomes have been reported on administration of antioxidants at the same time as, before and after the chemotherapeutic or radiation therapy. Therefore, incessant efforts using a diverse range of antioxidants are indeed warranted to establish the prophylactic and therapeutic efficacy of antioxidants in various types of cancer. Additionally, because the safety limits of antioxidants, especially from natural origin, are mostly unknown, efforts must be undertaken to consolidate this vital information database. In lieu of the prior literature, it can only be deciphered that administration of supplemental antioxidants during chemo- and/or radio-therapy should be dissuaded, because of the possibility of tumor protection and reduced survival. Small-scale clinical trials should preferably be based upon the biochemical activity, and the obtained results should be used during simultaneous treatment before commencing the large-scale trials. Hence, one should not recommend these antioxidants or vitamins indiscriminately to the patients for prophylaxis of cancer, until their definitive causal role has been ratified by further trials [27]. A maintenance dose of antioxidants, before or after the chemotherapy, could be recommended, however.

## Conflicts of interest

There are no conflicts of interest or disclosures associated with the manuscript.

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Please cite this article in press as: Khurana, R.K. et al. Administration of antioxidants in cancer: debate of the decade, Drug Discov Today (2018), https://doi.org/10.1016/j.drudis.2018.01.021