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Review

Antioxidants as precision weapons in war against cancer chemotherapy induced toxicity – Exploring the armoury of obscurity

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ABSTRACT

Cancer is the leading cause of mortality worldwide, accounting for almost 13% of deaths in the world. Among the conventional cancer treatments, chemotherapy is most frequently carried out to treat malignant cancer rather than localised lesions which is amenable to surgery and radiotherapy. However, anticancer drugs are associated with a plethora of side effects. Each drug, within every class, has its own set of adverse reactions which may cause patient incompliance and deterioration of the quality of life. One of the major causes of adverse reactions, especially for drugs targeting DNA, is the excessive production of reactive oxygen species (ROS) and subsequent build up of oxidative stress. To curb these undesired side effects, several dietary supplements have been tested, amongst which antioxidants have gained increasing popularity as adjuvant in chemotherapy. However, many oncologists discourage the use of antioxidant rich food supplements because these may interfere with the modalities which kill cancer by generating free radicals. In the present review, all studies reporting concomitant use of several antioxidants with chemotherapy are indiscriminately included and discussed impartially.

The effect of supplementation of thirteen different antioxidants and their analogues as a single agent or in combination with chemotherapy has been compiled in this article. The present review encompasses a total of 174 peer-reviewed original articles from 1967 till date comprising 93 clinical trials with a cumulative number of 18,208 patients, 56 animal studies and 35 *in vitro* studies. Our comprehensive data suggests that antioxidant has superior potential of ameliorating chemotherapeutic induced toxicity. Antioxidant supplementation during chemotherapy also promises higher therapeutic efficiency and increased survival times in patients.

Contents

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1. Introduction

Antioxidants prevent cellular damage by reacting and eliminating oxidizing free radicals thereby finding relevance in adjuvant chemotherapy. The use of antioxidant supplements by patients with cancer is estimated to be between 13 and 87% (VandeCreek et al., 1999; Block et al., 2008). Such broad range of percentage might be attributed to the difference in cancer types, age, education, complementary medicines and ethnicity in the group undertaken for the study. The use of supra-dietary doses of antioxidant has attracted increasing interest as a possible primary and secondary cancer deterrence strategy. Higher levels of endogenous antioxidant may protect against chemotherapy induced oxidative stress especially in some cancer patients having impaired capacity to deal with oxidative insult (Conklin, 2004). However, in cancer chemotherapy, a mode of action of certain antineoplastic agents involves generation of free radicals further leading to cellular damage and necrosis of malignant cells. Hence use of antioxidant during chemotherapy is criticized due to fear of causing interference with efficacy of the drug. On the contrary, many integrative practitioner converse uses of antioxidant supplements allowing patients to tolerate possibly higher effective doses of chemotherapy thereby increasing the chance of better tumor response and improved survival rate. Thus concomitant use of antioxidant during chemotherapy is been highly controversial topic. The questions repeatedly put forth are "Do antioxidants increase or decrease the efficacy of anticancer agent? Do antioxidants protect normal tissue and ameliorate toxicity or protect cancer cells from the effect of chemotherapy". This review intends to give a succinct idea about chemotherapy induced toxicity; ROS and oxidative damage followed with clarification on the major issue surrounding this controversy by reviewing the current state of understanding about potential and established interaction between antioxidant and conventional oncological therapies.

1.1. Chemotherapy

Chemotherapy is used primarily to treat systemic disease rather than localized lesions that are amenable to surgery or radiation. It uses antineoplastic agents in an attempt to destroy tumor cells by interfering with cellular function including replication. These drugs result in causing lethal injury to DNA which further leads to malignant cell death via apoptosis. In cancer treatment, mode of action of certain chemotherapeutic agents involves generation of free radicals to cause cellular damage and necrosis of malignant cells (Lamson and Brignall, 1999; Potmesil, 1994). Drugs with free radical mechanism include but are not limited to alkylating agent (alkylsulfonates, ethyleneamines and hydrazines), anthracyclines (doxorubicin and doxorubicin), platinum coordination complexes (cisplatin, carboplatin), podophyllin derivatives (etoposides) and camptothecins (irinotecan, topotecan). These ROS often are sources of atrocious side effects which remains as long as the duration of chemotherapy treatment (Joensuu, 2008).

1.2. Chemotherapy induced systemic toxicity

By its very nature, anti-cancer chemotherapy is cytotoxic that means it is designed to damage human cells. Because anti-cancer drugs are cytotoxic for normal as well as neoplastic cells, the range of unwanted effects that accompanies their use is broad. Many of the side-effects are potentially life-threatening or seriously debilitating. The precursor cells of the hemopoietic system, sited in the bone marrow, undergo cell division more rapidly than those of any other organ system and thus are particularly vulnerable to damage from cytotoxic drugs, since most chemotherapeutic agents act principally on dividing cells. Accordingly, bone marrow depression is a side-effect of nearly all such drugs and is the dose-limiting side effect of most. Red blood cell macrocytosis is a common effect of hydroxyurea, methotrexate, cytarabine and other antimetabolites.

Nausea and vomiting which usually occurs within 24 h of drug administration can be amongst the most disturbing and unpleasant side effects induced by chemotherapy. If persistent, vomiting may lead to dehydration, electrolyte disturbances, metabolic alkalosis, weakness, weight loss, cachexia, nutritional impairment and physical injury such as esophageal tears and fractures (Tortorice and Connell, 1990). Diarrhea and constipation in cancer patients may be due to many factors that include age, anticholinergics, narcotics, low fibre diet, decreased appetite and inability to eat and drink due to oral mucositis or esophagitis apart from the side-effects of cytotoxic drugs.

Cardiac damage is the dose-limiting toxicity of the anthracycline group of antitumor antibiotics related anthraquinones and can cause cumulative cardiomyopathy (Von Hoff et al., 1979). Damage to the liver is a complication of many drugs. Since patients receiving chemotherapy often are very ill and simultaneously receiving other medications that may impair liver function, it is often impossible to determine which of their treatments is responsible for the liver abnormality. Furthermore, septicemia, parenteral nutrition, viral and fungal infections and metastatic disease itself also commonly cause hepatic disturbance.

Pulmonary complications and kidney toxicity are being increasingly recognized and may be dose-limiting. Lung toxicity induced by methotrexate is said to occur in 5–8% of patients and includes pulmonary edema, pulmonary fibrosis, capillary leakage and hypersensitivity reaction (Bannwarth et al., 1994). The kidneys are vulnerable to damage from chemotherapeutic agents as they are the elimination pathway for many drugs and their metabolites. Cisplatin primarily causes proximal and distal tubular damage, although a rare hemolytic-uremic syndrome has also been reported (Daugaard et al., 1988).

Fertility problems can be an unfortunate delayed side effect of chemotherapy. Cytotoxic drugs damage the germinal epithelium resulting in reduced testicular volume and sperm count (Miller, 1971). The degree of dysfunction depends on the dose of drug as well as age and pubertal status of the patient at the time of treatment (Sherins, 1993). Often chemotherapy mediated toxicities are related to generation of ROS leading to oxidative stress in cell.

1.3. Chemotherapy induced ROS and their intracellular sources

Most of the oxygen taken up by the cells is converted to water by the action of cellular enzymes. However, some of these enzymes leak electron into oxygen molecules and lead to the formation of free radicals. They are also formed during normal biochemical reactions involving oxygen. ROS is a collective term used for a

group of oxidants, which are either free radicals or molecular species capable of generating free radicals. There are two important sources of free radical formation. First the internal factors i.e. normal cellular metabolism like mitochondrial electron transport chain (ETC), endoplasmic reticulum oxidation and many enzymic activities. Other exogenous factors are radiation, chemotherapy, cigarette smoke and oxygen itself (Shinde et al., 2012).

Intracellular free radical mainly comprises superoxide radicals ($O_2^{\cdot-}$), hydroxyl radicals ($OH^{\cdot-}$), nitric oxide ($NO^{\cdot}$), nitrogen dixiode ($N_2O^{\cdot}$) and lipid peroxyl ($LOO^{\cdot}$) radicals (Genestra, 2007). Under normal physiological conditions, nearly 2% of the oxygen consumed by the body is converted into $O_2^{\cdot-}$ through mitochondrial respiration, phagocytosis, etc. (Kunwar and Priyadarsini, 2011). Autooxidation of ubisemiquinone is the major source of superoxide anion (Han et al., 2001). Non radical or enzymic generation involves almost all oxidase enzymes (glycolate oxidase, D- amino acid oxidase, urate oxidase, acetyl-CoA oxidase, NADH oxidase and monoamine oxidase) generating H_2O_2 (Pourahmad, 2002).

$NO^{\cdot}$ is an endothelial relaxing factor and neurotransmitter, produced through nitric oxide synthase enzymes. $NO^{\cdot}$ and $O_2^{\cdot-}$ radicals are converted to powerful oxidizing radicals like hydroxyl radical ($^{\cdot}OH$), alkoxy radical ($RO^{\cdot}$), peroxyl radical ($ROO^{\cdot}$), singlet oxygen ($^1O_2$) by complex transformation reactions. Some of the radical species are converted to molecular oxidants like hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^-$) and hypochlorous acid (HOCl). Sometimes these molecular species act as sources of ROS. $HO^{\cdot}$ radical formation requires a cellular steady state level of both superoxide anion and H_2O_2, precursors of hydroxyl radicals via Fenton reaction. $ONOO^-$ at physiological concentrations of carbon dioxide becomes a source of carbonate radical ($CO_3^{\cdot-}$) anion (Winterbourn, 2008). Thus, chemotherapy becomes a substantial but indirect source of generating free radicals resulting into oxidative damage.

1.4. ROS induced oxidative damage

Depending upon their nature, chemotherapy induced ROS reacts with biomolecules to produce different types of secondary radicals like lipid, sugar, nitrogenous base, amino acid derived radicals and thiyl radicals [13]. These radicals in presence of oxygen are converted to peroxyl radicals that often induce chain reactions. The biological implications of such reactions depend on several factors like nature of the substrate, site of generation, activation of repair mechanisms, redox status etc (Winterbourn, 2008).

Cellular membranes are vulnerable to the oxidation by ROS due to the presence of high concentration of unsaturated fatty acids in their lipid components. ROS reactions with membrane lipids cause lipid peroxidation, resulting in formation of lipid hydroperoxide (LOOH) which can further decompose to an aldehyde such as malondialdehyde, 4-hydroxy nonenal (4-HNE) or cyclic endoperoxide, isoprotans and hydrocarbons. The consequences of lipid peroxidation are cross linking of membrane proteins, change in membrane fluidity and formation of lipid-protein, lipid-DNA adduct which may be detrimental to the functioning of cell (Conklin, 2004).

The side chains of all amino acid residues of proteins, in particular tryptophan, cysteine and methionine are susceptible to oxidation by ROS. Protein oxidation products are usually carbonyls such as aldehydes and ketones. Proteins can undergo direct and indirect damage following interaction with ROS resulting into peroxidation, changes in their tertiary structure, proteolytic degradation, protein-protein cross linkages and fragmentation (Beckman and Ames, 1997).

Although DNA is a stable and well-protected molecule, ROS can interact with it and cause several types of damage such as modification of DNA bases, single and double strand DNA breaks, loss of purines, damage to the deoxyribose sugar, DNA-protein cross-linkage and damage to the DNA repair systems (Beckman and Ames, 1997). Free radicals can also attack the sugar moiety, which can produce sugar peroxyl radicals and subsequently inducing strand breakage. The consequence of DNA damage is the modification of genetic material resulting in cell death, mutagenesis and ageing.

1.5. Redox state and oxidative stress

All forms of life maintain a steady state concentration of ROS determined by the balance between their rates of production and removal by various antioxidants. Each cell is characterized by a particular concentration of reducing species like GSH, NADH, $FADH_2$ etc., stored in many cellular constituents, which determine the redox state of a cell (Kohen and Nyska, 2002). By definition, redox state is the total reduction potential or the reducing capacity of all the redox couples such as GSSG/2GSH, NAD^+/NADH found in biological fluids, organelles, cells or tissues (Schafer and Buettner, 2001). Redox state not only describes the state of a redox pair, but also the redox environment of a cell. Under normal conditions, the redox state of a biological system is maintained towards more negative redox potential values. However, this balance can be disturbed when level of ROS exceeds and/or levels of antioxidants are diminished. This state is called 'oxidative stress' and can result in serious cellular damage or apoptosis of normal cells if the stress is massive and prolonged (Pham-Huy et al., 2008).

In contrast to oxidative stress-induced apoptosis, excessive oxidative stress inhibits caspase activity and drug-induced apoptosis, thereby interfering with the ability of antineoplastic agents to kill tumor cells. Electrophilic aldehydes, such as tetrapeptide aldehyde (acetyl-Tyr-Val-Ala-Asp-H) that are used to characterize caspase-1, covalently bind to the sulfhydryl group of the cysteine residue at the active site of caspases and inhibit their activity. Thus during oxidative stress, aldehyde generation resulting in caspase inhibition may account for the reduced efficacy of antineoplastic agents. If so, antioxidants may enhance the anticancer activity of cancer chemotherapy by reducing aldehyde generation during chemotherapy-induced oxidative stress (Conklin, 2004).

2. Antioxidant system

In order to check the activities of ROS/RNS *in vivo* and maintain cellular redox homeostastis, antioxidant system has evolved. Antioxidants are substances that may protect cells from the damage caused by free radicals, and may play a role in heart disease, cancer and other diseases. Antioxidants neutralize free radicals by donating one of their own electrons and ending the electron "stealing" reaction. This helps to prevent ROS mediated cell and tissue damage. Antioxidants are often described as "mopping up" free radicals, meaning they neutralize the electrical charge and prevent the free radical from taking electrons from other molecules (Bjelakovic, 2007).

Endogenous compounds in cells can be classified as enzymatic antioxidants such as superoxide dismutase, catalase, glutathione dependent enzymes and non-enzymatic antioxidants, further divided into metabolic and nutrient antioxidants. Metabolic antioxidants belonging to endogenous antioxidants such as GSH, lipoic acid, L-arginine, coenzyme Q10, melatonin, uric acid, bilirubin etc. are produced by metabolism in the body. Nutrient antioxidant belonging to exogenous antioxidants which are taken through food supplements are vitamin E, vitamin C, carotenoids, trace elements, flavonoids, polyphenols etc. (Valko et al., 2007; Alexieva et al., 2010). A delicate balance exists between antioxidant repairing systems and pro-oxidant mechanism of tissue

destruction, which if tipped in favour of cellular damage, could lead to significant tissue mutilation (Sharma and Sharma, 2011).

2.1. Chemotherapy, oxidative stress and antioxidants

Chemotherapy drugs that cause high levels of oxidative stress are thought to rely, in part, on using this stress mechanism to kill cancer cells. But oxidative stress might actually reduce the overall effectiveness of chemotherapy. Oxidative stress slows the process of cell replication, but it is during cell replication that chemotherapy actually kills cancer cells, so slower cell replication can mean lower effectiveness of chemotherapy (Conklin, 2004). One approach towards addressing this problem is the addition of certain antioxidants at specific dosages to lessen oxidative stress, thus making the chemotherapy treatment more effective (Perumal et al., 2005). The interaction between chemotherapy and antioxidants is more complex than simply promoting and inhibiting oxidative stress. However, there are several mechanisms by which chemotherapy functions and antioxidants also have a number of different effects on the body. Each antioxidant has a different interaction in chemotherapy and this effect can even change based upon the dosage used.

Some antioxidants have been found to be useful for restoring the natural antioxidants in the body, which are often depleted after the completion of chemotherapy, resulting in decreased side effects and increased the survival time in patients undergoing chemotherapy. Thus, targeted nutrient therapies using antioxidant or their precursors can prove to be beneficial in reducing the toxic effect of medications thereby improving the therapeutic efficacy.

2.2. Antioxidants in chemotherapy

Role of antioxidants are controversial in cancer therapy because of two very imperative features "First, there are two different kinds of antioxidants doses used based on which the data on the role of antioxidants in cancer therapy can be categorized as: a preventive dose, which is a low dose, and a therapeutic dose, which is a high dose. For the preventive dose, the data has shown protection of normal cells and tumor cells. For the therapeutic dose, the data shows that it inhibits the growth of cancer cells but not the normal cells. Therefore researchers are looking at data for preventive doses, which is perplexing.

Numerous original research articles have focused on the topic of whether supplemental antioxidants administered during chemotherapy can protect normal tissue without adversely influencing tumor control. Due to variation in study design, intervention protocol, cancer type, timing of observation, inclusive criteria, statistical analysis, chemotherapy regime develops uncertainty to make definitive conclusion regarding the risk of decreased tumor control as a consequence of administering supplemental antioxidant during chemotherapy. On the contrary certain recent review definitely concludes that that antioxidant when given concurrently (a) do not interfere with chemotherapy, (b) enhance the cytotoxic effect of chemotherapy, (c) protects normal tissue and (d) increases patient survival and therapeutic response (Simone et al., 2007a; Simone et al., 2007b).

Moss in the year 2007, investigated articles and reviews to find out the use of α-tocopherol for the amelioration of radiation-induced mucositis; pentoxifylline and vitamin E to correct the adverse effects of radiotherapy; melatonin alongside radiotherapy in the treatment of brain cancer; retinol palmitate as a treatment for radiation-induced proctopathy; a combination of antioxidants (and other naturopathic treatments) and the use of synthetic antioxidants like amifostine and dexrazoxane, as radioprotectants. With few exceptions, most of the studies draw positive conclusions about the interaction of antioxidants and radiotherapy (Moss, 2007).

Currently, evidence is growing that antioxidants may provide some benefit when combined with certain types of chemotherapy. Because of the potential for positive benefits, a randomized controlled trial evaluating the safety and efficacy of adding antioxidants to chemotherapy in newly diagnosed ovarian cancer is underway at the University of Kansas Medical Center (Drisko et al., 2003). In Long Island breast cancer patient study project, Greenlee and colleagues have reported that among 764 patients, 663 (86.8%) were found to be receiving adjuvant treatment for their breast cancer. Of those 663 women, 401 (60.5%) reported using antioxidants during adjuvant treatment. 210 of 310 women (38.7%) used antioxidants during chemotherapy, 196 of 464 women (42.2%) used them during radiation, and 286 of 462 women (61.9%) used them during tamoxifen therapy (Greenlee et al., 2009). In year 2012, same group published a data investigating the associations between antioxidant use after breast cancer diagnosis and breast cancer outcomes in 2264 women. Antioxidant supplement use after diagnosis was reported by 81% of women. Among antioxidant users, frequent use of vitamin C and vitamin E was associated with decreased risk of BC recurrence, vitamin E use was associated with decreased risk of all cause mortality but conversely, frequent use of combination carotenoids was associated with increased risk of death from breast cancer and all cause mortality (Greenlee et al., 2012).

A report on population-based prospective cohort study of 4877 women was conducted in the first 6 months after breast cancer diagnosis and during cancer treatment with total mortality and recurrence. Vitamin use shortly after breast cancer diagnosis was found to be associated with reduced mortality and recurrence risk, adjusted for multiple lifestyle factors, sociodemographics, and known clinical prognostic factors. Researchers concluded that vitamin supplement use in the first 6 months after breast cancer diagnosis may be associated with reduced risk of mortality and recurrence (Nechuta et al., 2011).

Cancer patients suffer from vitamin deficiencies, particularly of folic acid, vitamin C, pyridoxine and other nutrients because of poor nutrition and treatment. Chemotherapy reduces serum levels of antioxidant vitamins and minerals due to lipid peroxidation and thus produces higher level of oxidative stress. Therefore, supplementation of certain antioxidants and nutrients can help to enhance the health status of patients undergoing continous regime of chemotherapy (Drisko et al., 2003). Vitamin E has been shown to decrease chemotherapy mediated toxicity and with omega-3 fatty acid increase survival time in terminal cancer patients. Other than suppressing free radical induced progression of lipid peroxidation in normal cells, vitamin E is also known to induce apoptosis in experimental tumor lines and increase the efficacy of chemotherapy (Lamson and Brignall, 1999).

Kline et al. have reported approximately 50 vitamin E analogues being synthesized and screened for their ability to induce human tumor cells to undergo apoptosis (Kline et al., 2004). Eleven vitamin E analogues exhibited to have potent anticancer properties. Liposome-formulated α-TEA administered to BALB/c mice by aerosol for 17 days significantly reduced subcutaneous injected mouse mammary tumor cells growth and lung metastasis. Tumor volume was reduced by 65% in comparison with the aerosol control. Schwenke concluded that dietary exposure to α-tocopherol may modestly protect women from breast cancer. Some reports have suggested that vitamin E succinate (VES) inhibits the growth of human breast cancer in culture by induction of DNA synthesis arrest, cellular differentiation and apoptosis (Schwenke, 2002). The authors here wish to emphasize that combinations not studied *in vivo* risk potential adverse reactions and should be monitored closely.

Table 1
Effect of fat and water soluble vitamin supplementation in combination with different chemotherapeutic agents in various clinical trials as well as *in vivo* and *in vitro* studies.

Antioxidant	Type of chemotherapy	Type of study (n)	Toxicity mitigation	Higher therapeutic response rate	Increased survival	Author (reference)
Vitamin A	Cyclophosphamide	Animal	Yes	Yes	Yes	Seifter et al. (1984)
β-carotene	Cyclophosphamide	Animal	–	Yes but decreased therapeutic effect in fibrosarcoma, no change in squamous carcinoma	–	Seifter et al. (1984)
Vitamin A, β-carotene	5-fluorouracil, Cyclophosphamide, 4-Hydroperoxycyclophosphamide, melphalan	Animal and *In vitro*	–	Yes	–	Teicher et al. (1994)
Vitamin A	Doxorubicin, Bleomycin, 5-fluorouracil, Methotrexate	Human (25)	Yes	Yes	More sensitive	Thatcher et al. (1980)
Vitamin A	Doxorubicin and Etoposide	*In vitro*	–	Yes	–	Doyle et al. (1989)
Vitamin A	Doxorubicin, Cisplatin and Vincristine	*In vitro*	–	Increased Cytotoxicity effect, Increased cell differentiation and more sensitive to DOX	–	Adwankar et al. (1991)
Vitamin A	Methotrexate	Animal	Yes	No difference	–	Nagai et al. (1993)
Vitamin A	Etoposide, Cisplatin	Human (22)	No difference	No difference	No difference	Kalemkerian et al. (1998)
Vitamin A	Vincristine	*In vitro*	–	Increased cytotoxic effect	–	Adwankar et al. (1991)
Vitamin A	Tamoxifen	Human	–	Yes	–	Recchia et al. (1998)
Vitamin A	Tamoxifen	Human (25)	–	Yes	–	Budd et al. (1998)
Vitamin A	5-fluorouracil, Bleomycin, Doxorubicin, Mitomycin-C	Human (100)	Yes	Yes	Yes	Israel et al. (1985)
Vitamin A	5-fluorouracil	Human (275)	Yes	Yes	–	Komiyama et al. (1985)
Vitamin A	Busulfan	Human (1 5 3)	Yes	Yes	Yes	Meyskens et al. (1993)
Vitamin A	Cisplatin, Vindesine, 5-fluorouracil, Interferon	Human (40)	Yes	Yes	Yes	Recchia et al. (1993)
Vitamin A	5-fluorouracil, Cisplatin	Human (23)	Yes	Yes	Yes	Recchia et al. (1993b)
Vitamin A	Cyclophosphamide, 5-fluorouracil, Vincristine, Prednisone, Methotrexate, Mitomycin-C, Mitoxantrone, Tamoxifen	Human (36)	Yes	Yes	Yes	Recchia et al. (1995)
Vitamin A	5-fluorouracil, Epirubicin, Mitomycin-C, Interferon, Tamoxifen	Human (22)	No difference	No difference	No difference	Recchia et al. (1992)
Vitamin A	Tamoxifen	Human (49)	Yes	Yes	Yes	Recchia et al. (1995)
β-Carotene	Vincristine, Methotrexate, Bleomycin	Human (20)	Yes	No difference	No difference	Mills EE et al. (1988)
β-carotene	Chemotherapy	Human (15)	Yes	Yes	Yes	Santamaria et al. (1996)
Vitamin C	Doxorubicin, Cisplatin, Paclitaxel	*In vitro*	–	Synergistically Increasing cytotoxic effect	–	Kurbacher et al. (1996)
Vitamin C	Vincristine	Animal	–	Yes	–	Taper et al. (1987)
Vitamin C	Vincristine	*In vitro*	–	Increased cytotoxic effect	–	Chiang et al. (1994)
Vitamin C	Doxorubicin	Animal	Yes	Yes	Yes	Shimpo et al. (1991)
Vitamin C	5-fluorouracil, Bleomycin	*In vitro*	–	Increased cytotoxic effect	–	Prasad et al. (1999)
Vitamin C	Methotrexate	Animal	Yes	–	–	Khedr et al. (2008)
Vitamin C	Cisplatin	Human (48)	No difference	–	–	Weijl et al. (2004)
Vitamin C	Cyclophosphamide, Methotrexate, 5-fluorouracil	Human (30)	–	Yes	–	Goel et al. (1999)
Vitamin C	Doxorubicin	Animal (30)	Yes	–	–	Swamy et al. (2011)
Vitamin E	Cyclophosphamide	Animal	–	Yes	–	Vinitha et al. (1995)
Vitamin E	Doxorubicin, 5-fluorouracil	Animal	Yes	Yes	–	Vinitha et al. (1995)
Vitamin E	Doxorubicin	*In vitro* and Animal	Yes	Cytotoxic effect	–	Chinery et al. (1997)
Vitamin E	Doxorubicin, Methotrexate, Vincristine	*In vitro* and Animal	Yes	Cytotoxic effect	–	Perez Ripoll et al. (1986)
Vitamin E	Cisplatin	Animal	–	Yes	–	Sue et al. (1988)
Vitamin E	Cisplatin	Human (30)	Yes	–	–	Argyriou et al. (2006)
Vitamin E	Cyclophosphamide, Doxorubicin, 5-fluorouracil	Human	No difference	No difference	–	Legha et al. (1982)

(*continued on next page*)

Table 1 (*continued*)

Antioxidant	Type of chemotherapy	Type of study (n)	Toxicity mitigation	Higher therapeutic response rate	Increased survival	Author (reference)
Vitamin E	Doxorubicin	Human (12)	Yes	Yes	–	Lenzhofer et al. (1983)
Vitamin E	Chemotherapy for acute myelogenous leukemia, transplant	Human (20)	Yes	Yes	–	Lopez et al. (1994)
Vitamin E	Doxorubicin	Human (16)	No Difference	No Difference	No Difference	Weitzman et al. (1980)
Vitamin E	13-Cis retinoic acid	Human (66)	Yes	Yes	Yes	Besa et al. (1990)
Vitamin E	13-Cis retinoic acid	Human (39)	Yes	–	–	Dimery et al. (1992)
Vitamin E	All trans retinoic acid, erythropoietin	Human (17)	Yes	Yes	–	Ganser et al. (1996)
Vitamin E	Cyclophosphamide, Adrianmycin, 5-fluorouracil	Human (21)	Yes	Yes	–	Durken et al. (1995)
Vitamin E	Doxorubicin, Nifedipine	Human (12)	Yes	Yes	–	Erhola et al. (1996)
Vitamin E	5-fluorouracil, Cisplatin, Doxorubicin, Arabinosyl cytosine	Human (18)	Yes	Yes	–	Wadleigh et al. (1992)
Vitamin E	Adrianmycin	Human (16)	No difference	No difference	–	Erhola et al. (1998)
Vitamin E	Adrianmycin	Human (18)	Yes	Yes	–	Wood et al. (1985)
Vitamin E	Doxorubicin	Animal	Yes	–	Yes	Myers et al. (1977)
Vitamin E	Doxorubicin	Animal	Yes	–	Yes	Sonneveld et al. (1978)
Vitamin E	Camptothecin	Animal	Yes	–	–	Singh et al. (2011, 2011a, 2011b, 2012)
Vitamin E	Camptothecin	*In vitro*	Yes	–	–	Singh et al. (2012b, 2013)
Vitamin E	Methotrexate	*In vitro*	Yes	–	–	Singh et al. (2012a)
Vitamin E	Doxorubicin	Animal	Yes	–	–	Geetha et al. (1990a, b, 1991)
Vitamin E	Bleomycin, 5- fluorouracil, Adrianmycin, Cisplatin,mutamycin, CCNU, DTIC, Chlorozotocin	*In vitro*	–	Yes	–	Prasad et al. (1999)
Vitamin E	Cisplatin	Human (27)	Yes	No difference	No difference	Pace et al. (2003)
Vitamin E	Cisplatin, Carboplatin, Oxaliplatin and combination	Human (2 0 7)	No difference	No difference	No difference	Kottschade et al. (2011)
Vitamin E	Paclitaxel	Human (32)	Yes	–	–	Argyriou et al. (2006)
Vitamin E	Doxorubicin	Animal	Yes	–	–	Geetha and Devi (1992)
High dose pyrridoxine	Chemotherapy	Human (6300)	Yes	Yes	Yes	Ladner and Salkeld (1988)
High dose pyrridoxine	Cisplatin, Hexamethylamine	Human (248)	Yes	–	–	Wiernik et al. (1992)
Menadione (Vitamin D analogue)	Mitomycin-C	Human (51)	Yes	Yes	–	Margolin et al. (1995)
Vitamin K_3	Chemotherapy	Human (14)	Yes	Yes	–	Nagourney et al. (1987)
Vitamin D and analogues (PRI-2191 AND PRI-2205)	5-fluorouracil	Animal	Yes	Yes	Yes	Milczarek et al. (2013)
Vitamin D_3	Cisplatin	*In vitro*	–	Yes	–	Bao et al. (2014)
Vitamin D analogues	Irinotecan	Animal	–	Yes	Yes	Milczarek et al. (2013)
Vitamin D analogues	Oxaliplatin	Animal	–	Yes	–	Milczarek et al. (2013)
Vitamin D analogue (PRI-2191)	Imatinib mesylate	*In vitro*	–	Yes	–	Switalska et al. (2012)
Vitamin K_2	Cisplatin	*In vitro*	Yes	Yes	–	Yoshida et al. (2003)
Vitamin K_3	Adrianmycin	*In vitro*	–	Yes	–	Parekh et al. (1991)
Vitamin B	3-ethoxy-2-oxobutyraldehyde Bis (thiosemicarbazone)	Animal	Yes	Yes	–	Crim et al. (1967)
Vitamin D analogues (PRI-1906 And PRI-1907)	Cyclophosphamide	Animal	Yes (at lower dose)	Yes	–	Wietrzyk et al. (2008)
Vitamin B complex	Gentamycin sulphate	Animal (16)	Yes	–	–	Bello et al. (2009)
Vitamin B	Cisplatin	Animal	Yes (decrease in ototoxicity)	–	–	Guneri et al. (2001)

(n) = number of subjects involved in clinical study.

The following tables summarize the effect of various antioxidants when combined with specific chemotherapeutic agents.

Table 1 represents data collected from total of seventy-five peer reviewed research articles which investigated the concurrent use of fat and water soluble antioxidants with chemotherapy. Amongst them total number of clinical trials is 36 which had involvement of 8047 patients (males and females both). Total number of articles on *in vitro* and animal model are 19 and 28 respectively. Table represents use of 5 different vitamins in their various forms along with 34 different chemotherapeutic agents in a specific combination. 21 research papers explore concurrent use of vitamin A with 14 different chemotherapeutic agents used individually or in combination.

Table 2
Effect of GSH, Melatonin and NAC supplementation in combination with different chemotherapeutic agents in various clinical trials as well as *in vivo* and *in vitro* studies.

Antioxidant	Type of chemotherapy	Type of study (n)	Toxicity mitigation	Higher therapeutic response rate	Increased survival	Author (reference)
GSH	Cyclophosphamide, Cisplatin	Human (79)	Yes	Yes	–	Di Re et al. (1993)
GSH	Cyclophosphamide, Cisplatin	Human (20)	Yes	Yes	–	Locatelli et al. (1993)
GSH	Epirubicin, Cisplatin, 5-fluorouracil	Human	–	–	–	Zhang et al. (1999)
GSH	Epirubicin, Cisplatin, 5-fluorouracil	Human (50)	–	Yes	–	Cascinu et al. (1988)
GSH	5-fluorouracil	Animal	Yes	No difference	–	Danysz et al. (1984)
GSH	5-fluorouracil	Animal	Yes	No difference	–	Danysz et al. (1983)
GSH	Cisplatin	Human (151)	Yes	Possible	No difference	Smyth et al. (1997)
GSH	Cisplatin	Human (24)	Yes	Possible	No difference	Cascinu et al. (1995)
GSH	Cisplatin, Carboplatin	Human (50)	Yes	Yes	Yes	Bohm et al. (1999)
GSH	Cisplatin, Cyclophosphamide	Human (35)	Yes	Yes	–	Bohm et al. (1991)
GSH	5-fluorouracil and Cisplatin	Human (11)	Yes	–	–	Cozzaglio et al. (1990)
GSH	Cisplatin, Cyclophosphamide	Human (40)	Yes	Yes	–	Di Re et al. (1990)
GSH	Cisplatin, Bleomycin	Human (12)	Yes	Yes	–	Leone et al. (1992)
GSH	Cyclophosphamide	Human	Yes	–	–	Nobile et al. (1989)
GSH	Cisplatin, Cyclophosphamide	Human (16)	Yes	–	–	Oriana et al. (1987)
GSH	Cisplatin	Human	Yes	–	–	Parnis et al. (1995)
GSH	Cisplatin	Human (16)	Yes	–	–	Plaxe et al. (1994)
GSH	Cisplatin	Human (54)	No difference	Yes	–	Bogliun et al. (1996)
GSH	Oxalipaltin, Leucovorin and 5-fluorouracil	Human (52)	Yes	No difference	–	Cascinu et al. (2002)
GSH	Cisplatin, 5-fluorouracil, Etoposide	Human (20)	Yes	No difference	No difference	Schmidinger et al. (2000)
GSH	Mitomycin-C, 5-ffluorouracil and Phenobarbital	Human (207)	No difference	No difference	Yes	Fujimoto et al. (1983)
GSH	Cisplatin	Human (33)	Yes	No difference	No difference	Colombo et al. (1995)
Melatonin	Cyclophosphamide	Animal	Yes	No change in therapeutic effect	–	Musatov et al. (1997)
Melatonin	Cisplatin, Etoposide	Human (70)	Yes	No difference	Yes	Lissoni et al. (1997)
Melatonin	Cisplatin, Etoposide	Human (20)	Yes	–	Yes	Ghielmini et al. (1990)
Melatonin	Epirubicin	Human (12)	Yes	–	–	Lissoni et al. (1999)
Melatonin	Tamoxifen	Human (14)	Yes	Partial	–	Lissoni et al. (1995)
Melatonin	Tamoxifen	Human (25)	Yes	Partial	Yes	Lissoni et al. (1996)
Melatonin	Interleukin-2	Human	–	Synergistic	–	Lissoni et al. (1994)
Melatonin	Cisplatin and Etoposide	Human (100)	Yes	Yes	–	Lissoni et al. (2003)
Melatonin	Non – small cell lung: Cisplatin, Etoposide and Gemcitabine Breast: Doxorubicin, Mitoxantrone and Paclitaxel; Gastrointestinal: 5 FU & folinic acid. Head and neck cancer: 5-fluorouracil and Cisplatin	Human (250)	Yes	Yes	Yes	Lissoni et al. (1993)
Melatonin	Irinotechan	Human (30)	No difference	No difference	–	Cerea et al. (2003)
Melatonin	Cytarabine, Daunorubicin, and Etoposide	*In vitro*	No difference	No difference	No difference	Mustafa et al. (2011)
Melatonin	Vincristine / Isophosphamide	*In vitro*	Yes	Yes	–	Casada-Zapico et al. (2010)
NAC	Isophosphamide	Human	Yes	No difference	–	Slavik and Saiers (1983)
NAC	Isophosphamide	Human	Yes	No difference	–	Holoye et al. (1983)
NAC	Cyclophosphamide	Animal	Yes	No difference	–	Levy and Vredevoe (1983) [150]
NAC	Cyclophosphamide	Animal	Yes	No difference	–	Harrison et al. (1983)
NAC	Cyclophosphamide	Animal	Yes	No difference	–	Palermo et al. (1986)
NAC	Doxorubicin	Human (24)	No difference	No difference	–	Myers et al. (1983), Unverferth et al. (1983)
NAC	Doxorubicin	Animal	Yes	No difference	–	Olson et al. (1983)
NAC	Doxorubicin	Animal	Yes	No difference	–	Schmitt-Graff and Scheulen (1986)
NAC	Cisplatin or BCNU or Doxorubicin or vincristine or camptothecin	*In vitro*	Possible	–	–	Roller and Weller (1998)
NAC	Cisplatin	*In vitro*	Possible		–	Miyajima et al. (1999)
NAC and sodium thiosulfate	Cisplatin	*In vitro*	Yes	–	–	Dickey et al. (2005)

(n) = number of subjects involved in clinical study; GSH (Glutathione); NAC (N-Acetylcystein).

Vitamin C has been used as an adjunct antioxidant in 9 research articles of which 5 articles report its excellent synergistic and increased therapeutic effect. 34 articles have investigated the effectiveness of vitamin E in cancer chemotherapeutics of which 28 articles states that drug induced toxicity was efficiently ameliorated due to supplementation of vitamin E. Only few research articles on vitamin D and its analogues (9), vitamin K (3) and vitamin B (5) was found. Of all 75 research articles, 53 articles (70%) reports remarkable antioxidant mediated toxicity mitigation and rest 27 reports suggest no changes in the data or toxicity related studies was not applicable in the report. Therapeutic response after co-administration of antioxidant was also studied and was found out that 49 (65%) research articles has mentioned that antioxidant supplementation increases therapeutic efficiency and 15 (20%) articles reports increase in survival time.

Table 2 represents data collected from a total of forty-six peer reviewed research article which explored the consequences of antioxidants like GSH, melatonin and NAC in chemotherapeutics. Amongst them total number of clinical trial is 32 which had participation of 1415 subjects male and female both. Total number of articles on *in vitro* and animal model are 5 and 8 respectively. These 3 antioxidants are used in specific combination with 22 different chemotherapeutic agents. The combination of GSH and chemotherapy is the most studied category in our results (23 out of 46). The antioxidant substances were described as either "glutathione" or reduced glutathione. 12 out of 46 reports suggested use of melatonin in cancer chemotherapy and rest 11 reports are on co-supplementation of NAC along with cancer treating drugs. Of all 46 reports, 35 (76%) articles states that antioxidant administration mitigates drug induced toxicity which indicate superior potential of all 3 antioxidant in clinical and *in vitro* settings. 12 (26%) reports confirms higher therapeutic response upon antioxidant supplementation, 4 reports have published possible or partial usefulness of these antioxidants during chemotherapy and rest 29 articles suggest no possible role of antioxidant in enhancing the therapeutic response. Few (6) reports also reveals increased survival of subjects when provided with antioxidant along with chemotherapy.

Table 3 represents data assembled from 26 peer-reviewed research article which focuses on understanding the role of antioxidants like Quercetin, Selenium and Coenzyme Q10 during chemotherapy. This data comprises of 6 clinical studies engaging 270 subjects (both male and female), 15 animal studies, and 8 studies on *in vitro* model. 10 different chemotherapeutic agents were used individually or in combination with above listed all three antioxidants. 5 research articles explain the effect of quercetin in chemotherapy of which all 5 research submissions suggests higher therapeutic response rate in presence of antioxidant. Out of 10 reports on selenium, 8 articles (80%) unfolded the fact of co-administration of selenium along with different chemotherapeutic agent results in superior mitigation of toxicity induced during ther-

Table 3
Effect of Quercetin, Selenium and Coenzyme Q10 supplementation in combination with different chemotherapeutic agents in various clinical trials as well as *in vivo* and *in vitro* studies.

Antioxidant	Type of chemotherapy	Type of study (n)	Toxicity mitigation	Higher therapeutic response rate	Increased survival	Author (reference)
Quercetin	Busulfan, Cisplatin	Animal and *In vitro*	–	Yes	–	Scambia et al. (1992)
Quercetin	Doxorubicin, Daunorubicin	*In vitro*	–	Increased cytotoxic effect	–	Scambia et al. (1994), Critchfield et al. (1994), Versantvoort et al. (1993)
Quercetin	Cisplatin	Animal and *In vitro*	–	Increased therapeutic effect& cytotoxic effect	–	Hofmann et al. (1990)
Selenium	Melphalan	*In vitro*	Yes	No difference	Increased number of viable cells	Tobey and Tesmer (1985)
Selenium	Doxorubicin	Animal	Yes	–	–	Boucher et al. (1995)
Selenium	Doxorubicin	Animal	Yes	–	–	Coudray et al. (1995)
Selenium	Doxorubicin	Animal	–	Yes	–	Shallom et al. (1995)
Selenium	Methotrexate	Animal	–	Yes	–	Milner et al. (1981)
Selenium	Cisplatin	Human (41)	Yes	–	–	Hu et al. (1997)
Selenium	Cisplatin	Animal	Yes	Yes	–	Naganuma et al. (1984)
Selenium	Cispltin	*In vitro*	Yes	Yes	–	Berry et al. (1984)
Selenium	Cisplatin	Animal	Yes	Yes	–	Ohkawa et al. (1988)
Selenium	Cyclophosphamide	Animal	Yes	Yes	–	Chakraborty et al. (2009)
Coenzyme Q10	Cyclophosphamide + Doxorubicin + 5-fluorouracil	Human (40) and Animal (Combined therapy)	Yes	Yes	–	Takimoto et al. (1982)
Coenzyme Q10	Cyclophosphamide + OK432	Animal (Combined therapy)	Yes	Yes	–	Kokawa et al. (1983)
Coenzyme Q10	Doxorubicin	Human (10)	Yes	No difference	–	Cortes et al. (1978)
Coenzyme Q10	Doxorubicin	Human (80)	Yes	No difference	–	Okuma et al. (1984)
Coenzyme Q10	Doxorubicin	Animal	Yes	No difference	–	Shaeffer et al. (1980)
Coenzyme Q10	Tamoxifen	Animal	–	Yes	–	Perumal et al. (2005)
Co-enzyme Q10	Doxorubicin	Human (79)	Yes	Yes	–	Tsubaki et al. (1984)
Co-enzyme Q10	Doxorubicin, Daunorubicin	Human (20)	Yes	–	–	Iarussi et al. (1994)
Coenzyme-Q10	Doxorubicin	Animal	Yes	–	–	El-Sheikh et al. (2012)
Coenzyme-Q10	Cisplatin	Animal (32)	Yes	–	–	Fouad et al. (2010)
Coenzyme-Q10	Doxorubicin	*In vitro*	Yes	No difference	–	Greenlee et al. (2012)

(n) = number of subjects involved in clinical study.

Table 4
Combinatorial effect of a mixture of antioxidants with different chemotherapeutic agents in various clinical trials as well as *in vivo* and *in vitro* studies.

Antioxidants	Type of chemotherapy	Type of study (n)	Toxicity mitigation	Higher therapeutic response rate	Increased survival	Author (reference)
Vit C and K3	Cyclophosphamide, Doxorubicin 5-fluorouracil	Animal	Yes	Yes	–	Taper et al. (1987)
Beta carotene, Vit A, Vit C, Vit E	Cisplatin, Tamoxifen, Interferon	*In vitro*	–	Increased cytotoxic effect	–	Prasad et al. (1994)
Vit A, Beta caotene, Vit E, Thiamine, Riboflavin, Pyridoxine, Vit B12, Vit D, VitC,Calcium and Biotin	Cyclophosphamide, Doxorubicin, Vincristine	Human (18)	Yes	Yes	Yes	Jaakkola et al. (1992)
Vit C, Vit E and GSH	Peplomycn, 5-fluorouracil	Human (63)	Yes	Yes	–	Osaki et al. (1994)
Vit A and Vit E	5-fluorouracil, Methotrexate, Leucovorin, Epirubicin	Human (41)	–	–	Yes	Pyrhonen et al. (1995)
Antioxidant nutrients	Chemotherapy (site appropriate)	Human (58)	Yes	Yes	–	Copeland et al. (1975)
Vit A, Beta carotene, Vit E and Selenium	Cyclophosphamide, Doxorubicin- HCl, Vincristine	Human (18)	Yes	Yes	Yes	Jaakkola et al. (1992)
Vit C, Vit E, Carotene and Selenium	Chemotherapy	Human (32)	Yes	Yes	Yes	Lockwood et al. (1994)
Vit C, E and Glutathione	5-fluorouracil, Peplomycin	Human (63)	Yes	Yes	–	Osaki et al. (1994)
Vit A and Vit E	5-fluorouracil, Epidoxorubicin, Methotrexate	Human (41)	Yes	–	Yes	Pyrhonen et al. (1995)
Vit A, Vit C and Vit E	Chemotherapy (site appropriate)	Human (20)	Yes	Yes	–	Sakamoto et al. (1983)
Vit A, Vit C, Vit E and Selenium	Chemotherapy	Human	Yes	–	–	Thiruvengadam et al. (1996)
Acetyl cysteine, Vit C and Vit E	Chemotherapy	Human (14)	Yes	–	–	Wagdi et al. (1995)
Vit C and Vit K	Cyclophosphamide, Vinblastine, Doxorubicin, 5-fluorouracil, Procarbazine, Asparginse	Animal	–	Yes	–	Chinery et al. (1997)
Vit C and Vit E	Mixed chemotherapy	Human (25)	No difference	No difference	No difference	Wagdi et al. (1996)
Antioxidant mixtrue, Vit C, Vit E and β-carotene	Carboplatin and Paclitaxel	Human (136)	No difference	No difference	No difference	Pathak et al. (2005)
Vit A, Vit E, Coenzyme Q10, Vit C, β- carotene	Carboplatin and Paclitaxel	Human (2)	Yes	Yes	–	Jeanne Drisko et al. (2003)
Vit C and E	5-fluorouracil, Doxorubicin, Cyclophosphamide	Human (40)	Yes	Yes	–	Suhail et al. (2012)
13-*cis*-retinoic acid and Vit D_3	5-fluorouracil	*In vitro*	–	Yes	–	Dalirsani et al. (2012)
Vit C and Vit E	Doxorubicin	Animal	Yes (dose dependent)	Yes (dose dependent)	–	Antunnes et al. (1998)
Riboflavin, Niacin and Co-enzyme Q10	Tamoxifen	Animal	Yes	Yes	–	Perumala et al. (2005)
Vit D_3 and Retinoic Acid	Cisplatin	*In vitro*	Yes	No decrease in tumor size	–	Jorgensen et al. (2013)

(n) = number of subjects involved in clinical study.

apies. Likewise out of 11 reports, 9 articles (81%) supports antioxidants supplementation in order to alleviate drug induced toxicity. Of total 26 reports, 18 articles (69%) corroborate the fact of antioxidant mediated toxicity mitigation and rest 8 articles published no change in the data or the study was not applicable. 15 articles (57%) showed antioxidant supplementation increases the therapeutic efficiency of the cancer drug possibly by having a synergistic effect whereas there were no reports on increased survival time in subjects or models used in studies.

In Table 4, data from twenty-two research submissions are incorporated which analyses the outcome of mixture of antioxidant along with cancer treating drugs. Many research article pose that mixture of antioxidants can be more beneficial than using this antioxidants individually. A total of 15 antioxidants in a specific combination at a particular dose were combined with a well scheduled chemotherapy regime including 17 different types of chemotherapeutic agents. This data represent 15 clinical trials including 571 subjects, 4 animal studies and 3 experiments on *in vitro* model. Out of 22, 16 articles (72%) emphasis on toxicity amelioration by antioxidant mixture during therapy, 15 research papers reports increased therapeutic response and 5 states there was increase in the survival time after antioxidant administration.

3. Conclusion

This review constitutes a total of 174 peer-reviewed original articles from 1967 till date comprising 93 clinical trials with a cumulative number of 18,208 subjects, 56 animal and 35 *in vitro* studies. Out of total cases reported in 174 research articles, 138 research papers have reported consequences of antioxidant supplementation during or after chemotherapeutic setting of which 122 articles (88%) states that antioxidants mitigates the toxicities induced by chemotherapeutic agents. Out of 130 papers, 91 articles (70%) reports that the therapeutic efficiency of chemotherapy increases in presences antioxidants. Conjugate antioxidant supplementation was also seen to increase the survival time in the patients according to 26 reports (63%) of 41 research article. Thus our comprehensive data therefore suggests that antioxidants do not interfere with chemotherapy and can be prescribed during clinical setting to increase the standard of life.

4. Discussion

The advent of modern cancer treatments has substantially improved the survival rate of patients. The enhancement in survival reflects progress in early stage diagnosis and use of combination chemotherapy. However, chemotherapeutic agents are associated with toxicity due to their potential to target rapidly dividing normal cells in the body. The prime concern of chemotherapy is drug associated oxidative stress, which results in many side effects.

Use of antioxidants can be beneficial in this respect as they minimize the burden of free reactive radicals in cells and thus can decrease the duration of chemotherapy regimens. Despite nearly two decades of research investigating the use of dietary antioxidant supplementation during conventional chemotherapy, controversy remains about the efficacy and safety of this complementary treatment. Several randomized clinical trials have demonstrated that the concurrent administration of antioxidants with chemotherapy reduces treatment-related side effects. Some data indicate that antioxidants may protect tumor cells as well as healthy cells from oxidative damage generated by some chemotherapeutic agents. However, other data suggest that antioxidants can protect normal tissues from chemotherapy induced damage without decreasing tumor control.

The lack of enthusiasm among clinical oncologists for using high doses of antioxidant vitamins in combination with chemotherapy is primarily based on fear that antioxidant vitamins may protect both normal and cancer cells against free radicals which are generated by most of the chemotherapeutic agents. Often there is disagreement on how could antioxidant therapy protect normal cells against damage from cancer therapies, while not affecting or increasing their cytotoxic effect against malignant cells? Answer to this question is not entirely figured out, but there are certain concepts which might help us understand. One is that if generation of ROS by cancer chemotherauptic agent or a free radical intermediate of the drug plays a role in its cytotoxicity, antioxidant may interfere with the drug's antineoplastic activity. However, if the reactive species are responsible only for drug's adverse effects, antioxidant may actually reduce the severity of such effect without interfering with the drug's antineoplastic activity. Thus, it is important to distinguish between a drug's ability to induce oxidative stress in biological system and the role, if any, that ROS or free radicals intermediate play in the mechanism of action of the drug. Second concept why antioxidants are found to increase drug's cytotoxic effect against malignant cells is that, chemotherapy often harms DNA, which causes the cells to undergo apoptosis, rather than necrosis. Since many antioxidant treatments stimulate apoptotic pathways, the potential exists for a complementary effect with chemotherapy and antioxidants. The third view is that, defensive mechanisms of many cancer cells are known to be impaired. This presumably makes tumor cells unable to use the extra antioxidants in a repair capacity.

The clinical cancer research community should cooperate and focus new studies on the use of a specific combination of antioxidant in chemotherapy, and determine optimal doses of antioxidant for a specific cancer setting. Mechanistic studies on the interaction between antioxidants and conventional cancer therapy could also lead to novel biomarkers for assessing dose adequacy.

Conflict of interest

Authors declare no conflict of interest. Authors declare full control of all primary data.

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