Archives of Business Research – Vol. 12, No. 4
Publication Date: April 25, 2024
DOI:10.14738/abr.124.16842.
Prasad, K. N. (2024). Therapeutic Doses of Antioxidants Inhibit the Growth and Enhance the Effects Chemotherapy and Radiation Therapy on Cancer Cells by Blocking the Uptake and Metabolism of Glucose and Glutamine. Archives of Business Research, 12(4). 104-122.

SERVICES FOR SCIENCE AND EDUCATION

Therapeutic Doses of Antioxidants Inhibit the Growth and Enhance the Effects Chemotherapy and Radiation Therapy on Cancer Cells by Blocking the Uptake and Metabolism of Glucose and Glutamine

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ABSTRACT

Chemotherapy and radiation therapy have produced increased 5-year survival rate in majority of cancers; however, acute side-effects during treatment and late adverse effects after these therapies remain a major concern of oncologists. To improve further 5-year survival rate and reduce acute and late adverse effects of therapies, a new non-toxic biological approach is needed. Experimental data for such an approach was available for over 25 years. For example, therapeutic doses of antioxidants inhibit the growth of cancer cells and enhances the growth-inhibitory effects of chemotherapeutic agents and x-irradiation on cancer cells but not on normal cells. These exciting observations failed to draw any attention from oncologists, because mechanistic data on therapeutic doses was not available until now. The mechanistic data on preventive doses of antioxidants suggested that they scavenge free radicals. Since one of the mechanisms of action of chemotherapy and radiation therapy on cancer cells is mediated by free radicals, oncologists fear that supplementation with antioxidants may reduce the effectiveness of cancer therapies by neutralizing free radicals. Cancer cells require glucose and glutamine for their survival and proliferation. This review briefly describes the effects of therapeutic doses of antioxidants alone and in combination with chemotherapy and radiation therapy on the growth of neoplastic cells and normal cells. It also presents evidence to show that such doses of antioxidants reduce the uptake and metabolism of glucose and glutamine in cancer cells. We propose that therapeutic doses of multiple antioxidants can selectively kill cancer cells and enhance the growth-inhibitory effects of therapeutic agents on cancer cells without affecting normal cells by inhibiting the uptake and metabolism of glucose and glutamine.

Keywords: Therapeutic doses of antioxidants, growth inhibition, glucose and glutamine uptake, cancer therapeutic agents.

INTRODUCTION

The levels of reactive oxygen species (ROS) produced by oxidative phosphorylation of mitochondria and nicotinamide adenine dinucleotide oxidases (NOXs) are generally higher in tumors than normal tissue, because they act a signal molecule for the growth and metastasis (1, 2). Maintenance of oxidative stress homoeostasis is essential for cancer cell survival and glutamine plays an important role in maintaining this function in cancer cells; however, excess production of free radicals destroys oxidative homeostasis causing damage to cancer cells (3,

4). Chemotherapy and radiation therapy produces excessive amounts of free radicals which disturb the oxidative homoeostasis of cancer cells that lead to death of these cells.

Chemotherapy and radiation therapy have increased 5-year survival after the diagnosis of majority of cancer. The increase in 5-year survival rate varies depending upon the type of tumor (from NIH, Division of Cancer Control and Population Sciences, 2023). Despite these treatments cancer death continues to increase. It is projected that in 2023, approximately 610,000 people would die from this disease, compared to 602,000 deaths in 2020, and 569,000 deaths in 2010. Furthermore, the adverse side-effects of chemotherapy and radiation therapy during and after treatment remains a major concern of oncologists. Damage to the normal tissues during chemotherapy and radiation therapy include loss of hairs, depressed immune response, loss of appetites, fatigues, and nausea. The late adverse effects of cancer treatment include recurrence of primary tumor, second primary cancers, damage to the brain**,** bone, endocrine system, eyes, hearing, heart, lung, joints, and mouth. They also include occurrence of lymphedema and post-traumatic stress disorder (PTSD) (Data were summarized from the National Institutes of Health: Late Effects of Cancer Treatment). The risk of recurrence markedly increased within 3 years of treatment and then labeled off except for breast cancer (5). Among cancer survivors, the risk of second primary tumors increases for lung cancer, prostate cancer, urinary bladder cancer, and colorectal cancer in men. In women, except for breast cancer, the incidence of lung cancer and colorectal cancer was lower than in men, and the incidence of uterine cancer remains less than 10% (6). Because of these adverse health effects of chemotherapy and radiation therapy, a new non-toxic biological approach that can further enhance 5-year survival rate of cancer therapies and reduce their acute and late adverse effects of therapies is needed. Although this new approach was available for over 35 years, it did not draw any attention from the oncologists. For example, several studies and reviews showed that therapeutic doses of individual and multiple antioxidants inhibited the growth of tumor cells and enhanced the growth-inhibitory effects of chemotherapy and radiation therapy on cancer cells without significantly affecting the growth of normal cells (7-13). Since no mechanistic data on the effect of therapeutic doses of antioxidant on cancer cells were known, oncologists feared that antioxidants, which are known to scavenge free radicals, may block the growth-inhibitory effects of chemotherapy and radiation therapy on cancer cells (14, 15). The observation in which vitamin C at preventive doses (low doses) stimulated the growth of some cancer cells in culture (16) may have further discouraged oncologists about using antioxidants during treatment of cancer.. While searching for the mechanisms of action of therapeutic doses of antioxidants on cancer cells, we found that all cancer cells irrespective of type and sensitivity to tumor therapeutic agents require the uptake and metabolism of glucose and glutamine for their survival and proliferation and high doses of antioxidants block the uptake and metabolism of glucose and glutamine. The references for these statements are provided in each section later in the manuscript.

This review presents evidence to show that therapeutic doses of antioxidants kill cancer cells and enhanced the growth-inhibitory effects of chemotherapeutic agents and x-irradiation on cancer cells without significantly affecting the proliferation of normal cells. Studies show that cancer cells require glucose and glutamine for their survival and growth, and that therapeutic doses of antioxidants block the uptake and metabolism of these nutrients. Based on evidence presented, I propose that oral administration of a mixture of micronutrients containing

URL: http://doi.org/10.14738/abr.124.16842

therapeutic doses of multiple antioxidants in combination with chemotherapy and/or radiation therapy may increase the 5-year survival rate of cancer patients more than that produced by the individual therapy, while reducing the acute and late adverse effects of therapies.

DIFFERENCE BETWEEN THERAPEUTIC AND PREVENTIVE DOSES OF ANTIOXIDANTS

A few examples of therapeutic doses of antioxidants in humans include vitamin C doses 5g/day or higher, vitamin E succinate doses 1600 IU or higher, vitamin A 10,000IU or higher, resveratrol 1000 mg or higher, whereas preventive doses include vitamin C 500 mg or less, vitamin A, 5000IU or less, vitamin E 60 mg or less, and resveratrol 50 mg or less.

THERAPEUTIC DOSES OF INDIVIDUAL ANTIOXIDANT INHIBIT THE GROWTH OF CANCER CELLS WITHOUT AFFECTING THE GROWTH OF NORMAL CELLS

Treatment with Vitamin C

In 1976, Dr. Linus Pauling and his colleagues were first to demonstrate that vitamin C at therapeutic doses inhibited the growth of cancer cells without affecting the growth of normal cells in humans (9, 17). This observation became controversial because others could not confirm their observation in cancer patients, in part, due to different in experimental design. However, we confirmed their work by showing that vitamin C at therapeutic doses killed all murine neuroblastoma (NB) cells in culture, whereas the growth of normal fibroblasts in culture was only minimally reduced. We further demonstrated that therapeutic doses of vitamin C enhanced the effects of certain chemotherapeutic agents and x-irradiation on neuroblastoma cells. This study also demonstrated that glioma cells were relatively less sensitive to vitamin C than neuroblastoma cell (7) (Table 1). We further demonstrated that vitamin C at therapeutic doses also inhibited the growth of human tumorigenic parotid acinar cells in culture but had no effect on the growth of non-tumorigenic parotid acinar cells (16).

Table 1: Effect of sodium L ascorbate (Na L-ascorbate) in combination with 5-Flurouracil (5-FUra) or x-irradiation on Neuroblastoma (NB) and Glioma cells in culture

Treatment	Cell No.% of control*	
	NB	Glioma
Na L-ascorbate	105 ± 9	98 ± 5
5-FUra	62 ± 5.	58 ± 6
Na L-ascorbate + 5- FUra	4.5 ± 2.1	45 ± 4
X-irradiation	28 ± 3	29 ± 3
Na L-ascorbate + X-irradiation	1.8 ± 0.4	27 ± 3

*Shown as mean ± SD ($n \geq 6$)

Cells (50,000 per dish) were plated in Falcon plastic dishes (60mm), and Na L-ascorbate, 5 μg/ml for NB cells, 100 μg/ml for glioma cells, and 5-FUra 0.08 μg/ml for NB cells, 0.3 μg/ml for glioma cells, and x-irradiation (400 rads or 4 Gy) were given 24 hr. after plating. The growth medium and treatment agents were changed every day. Th effect of 5-FUra on cell number was determined 3days after treatment; and the effect of x-irradiation was determined 4 days after irradiation.

Treatment with D-alpha-tocopheryl Succinate (vitamin E succinate)

In 1982, we discovered that vitamin E succinate at therapeutic doses induced differentiation and growth inhibition in murine melanoma cells in culture (8) (Figure 1). Vitamin E succinate at a growth-inhibitory dose reduced the expression of oncogenes c-myc and H-ras in melanoma cells in culture (18). Several studies using other cancer cell lines in culture and in animal models of cancer confirmed this observation (10, 19-22). A recent review has further documented the role of vitamin E succinate in inhibiting the growth of tumor cells (23).

Treatment with Beta-Carotene or Retinol

Administration of beta-carotene or retinol treatment at therapeutic doses induced differentiation in murine NB cells and B-16 murine melanoma cells in culture, respectively, and inhibited their growth (24).

Treatment with Quercetin

Overexpression of cyclooxygenase (COX-2) plays a significant role in the development and progression of cancer. Treatment with quercetin at a therapeutic dose increased apoptosis and inhibited the growth of human colon cancer cells (HT29 cells) over-expressing Cox-2 enzyme, but it was less effective in HCT 15 cell line expressing reduced level of COX-2 enzyme and had no significant effect on normal epithelial cell line (IEC-6) (25).

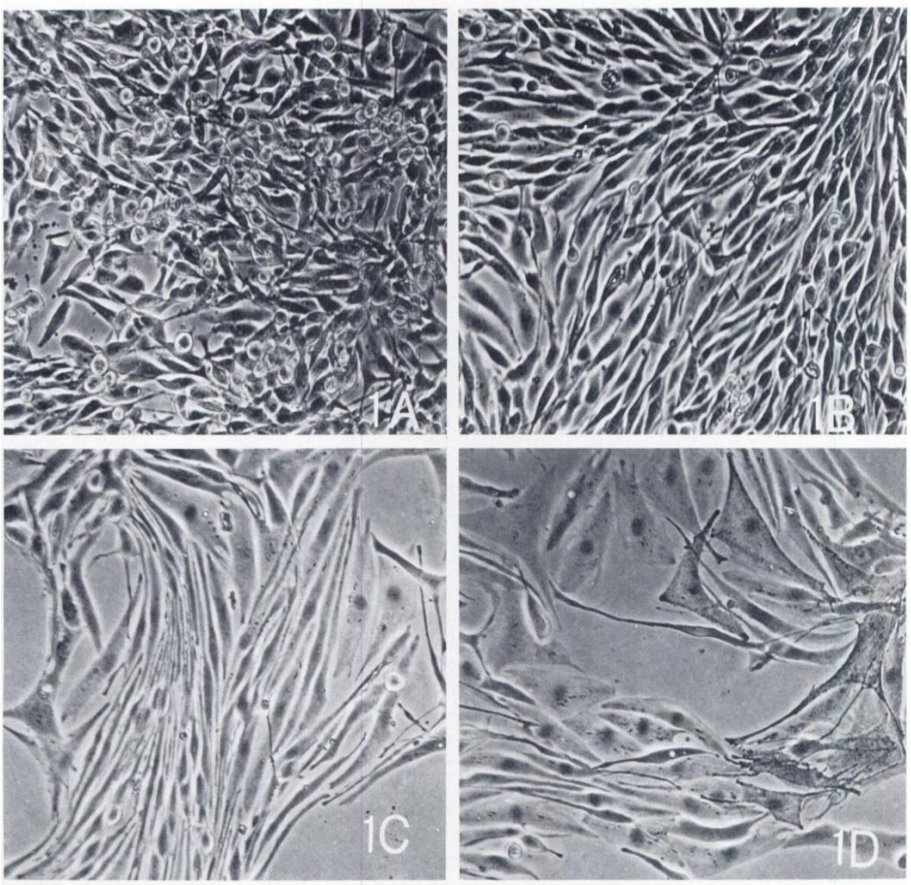


Figure 1: Melanoma cells (10^5) were plated in tissue culture dishes (60 mm), and *d*-alpha-tocopheryl succinate (α-TS) and sodium succinate plus ethanol were added to separate cultures

URL: http://doi.org/10.14738/abr.124.16842

24 h after plating. Vitamin E and medium were changed at 2 and 3 d after treatment. Photomicrographs were taken 4 d after treatment. Control cultures showed fibroblastic cells as well as round cells in clumps (1A); cultures treated with ethanol (1%) and sodium succinate (5-6 µg/ml) also exhibited fibroblastic morphology with fewer round cells (1B); α-TS-treated cultures 6 µg/ml (1C), and 8 µg/ml (1D) showed a dramatic change in morphology, Mag.X300(8).

Treatment with Resveratrol

Administration of resveratrol reduced the growth of human leiomyoma cells in culture and in rat-derived uterine leiomyoma transplanted in athymic mice (26).

Treatment with Coenzyme Q10

The effectiveness of coenzyme Q10 on human cancer remains controversial. Daily supplementation of coenzyme Q10 at a therapeutic dose of 390 mg or more may increase the survival of breast cancer patients receiving standard cancer therapy (27-29). On the other hand, another clinical study on breast cancer revealed that administration of 300 mg coenzyme Q10 did not improve fatigue or the quality of life during treatment (30)

Treatment with Curcumin

Administration of curcumin at a therapeutic dose reduced the growth and caused apoptosis in various cancer cells in culture (31, 32). Curcumin treatment markedly reduced the growth of gastric carcinoma and suppressed gastric-mediated secretion, which inhibited the progression of gastric cancer cells (33) Curcumin treatment also reduced proliferation of human colon cancer cells in culture (34).

ANTIOXIDANT MIXTURES INHIBITED THE GROWTH OF CANCER CELLS WITHOUT AFFECTING THE GROWTH OF NORMAL CELLS

Treatment with a mixture of antioxidants containing ascorbic acid, quercetin, green tea extract, lysine, and proline inhibited the growth of human ovarian cells in culture and in athymic mice (35). The elimination of quercetin from this mixture did not affect its potency inhibiting the growth of human retinoblastoma cells in culture and in athymic mice (36), human leukemic cell line U-93, and head and neck squamous cell carcinoma cell line FaDu in culture and in athymic mice (37). Administration of another antioxidant mixture containing quercetin, curcumin, resveratrol, green tea extract, and cruciferex also reduced the growth of human Faconi anemia head and neck squamous cell carcinoma in culture (OHSU-974 cell line) and in athymic mice, and in fibrosarcoma (HT-180 cell line) and melanoma (A2058 cell line) (38). A mixture of antioxidants containing vitamin C, vitamin E, and beta-carotene enhanced the cytotoxic effects of combined treatment with paclitaxel and carboplatin on human lung squamous cell carcinoma cell line H520 (39). Another mixture of antioxidants containing vitamin C, retinoic acid, polar carotenoids, and d-alpha-tocopheryl succinate at non-growth-inhibitory dose inhibited the growth of human melanoma cells in culture by about 50% (Table 2). It is significant that when any of the above four antioxidants were used individually, they had no effect on the growth of human melanoma cells in culture, but when they were used in combination, they produced about 50% growth inhibition in human melanoma cells in culture. This suggests that antioxidants in the mixture interact with each other to reduce the growth of cancer cells. In addition, increasing the dose of vitamin C to therapeutic dose level in the mixture dramatically

reduced the growth of melanoma cells. This suggests that therapeutic doses of all four antioxidants might have produced more dramatic inhibition of growth of these cells. The same antioxidant mixture reduced the growth of tumorigenic parotid acinar cells (2HP1G) without significantly affecting that of growth of non-tumorigenic parotid acinar cells (2HPC8) in culture (16).

Table 2: Effects of a mixture of 4 antioxidants on the growth of human melanoma cells in culture (SK-30 cells)

Treatments	Growth (% of control)
Vitamin C (50 µg/ml)	102 ± 5a
Polar Carotenoids (10 µg/ml)	96 ± 2
Alpha-tocopheryl succinate (10 µg/ml)	102 ± 3
13-cis Retinoic acid (7.5 µg/ml)	103 ± 3
A mixture of 4 antioxidants	56 ± 3
Vitamin C (100 µg/ml)	64 ± 3
A mixture of 4 antioxidants with vitamin C 100 µg/ml)	13 ± 1

Cells were plated in tissue culture dishes, and antioxidants were added 24 h later. Fresh growth medium and antioxidants were changed 2 days after treatment and cell number was counted 3 days after treatment, Growth was determined as % of untreated control. Each experiment was repeated 3 times involving 3 samples per treatment group. Data were taken from a previous publication (49).

EFFECTS OF THERAPEUTIC DOSES OF INDIVIDUAL ANTIOXIDANTS IN COMBINATION WITH CHEMOTHERAPEUTIC AGENTS AND X-IRRADIATION

Vitamin A and beta-carotene

Administration of vitamin A or beta-carotene produced one-year survival in x-irradiated mice with transplanted adenocarcinoma compared to no survival in x-irradiated controls (40). Oral administration of beta-carotene reduced radiation-induced oral mucositis without interfering with the efficacy of radiation therapy in patients with head and neck cancer (41).

Vitamin C

As early as in 1979, treatment with vitamin C as sodium ascorbate enhanced the growth-inhibitory effects of x-radiation and certain chemotherapeutic agents on neuroblastoma cells in culture (7). For example, vitamin C enhances the growth-inhibitory-effect of 5-FU (5-Fluorouracil) in neuroblastoma cells in culture (Figure 2). Daily administration of Vitamin C at a therapeutic dose reduced oxidative stress in patients with differentiated thyroid cancer receiving radioiodine therapy; however, its effectiveness in enhancing the efficacy of radioiodine therapy was not evaluated (42). Intravenous administration of therapeutic doses of vitamin C in combination with gemcitabine and radiation therapy increased overall survival time in patients with pancreatic cancer compared to individual therapy. This study also demonstrated that therapeutic doses of ascorbate sensitize the effect of radiation on pancreatic cancer cells but inhibited radiation-induced damage to normal cells (43, 44).

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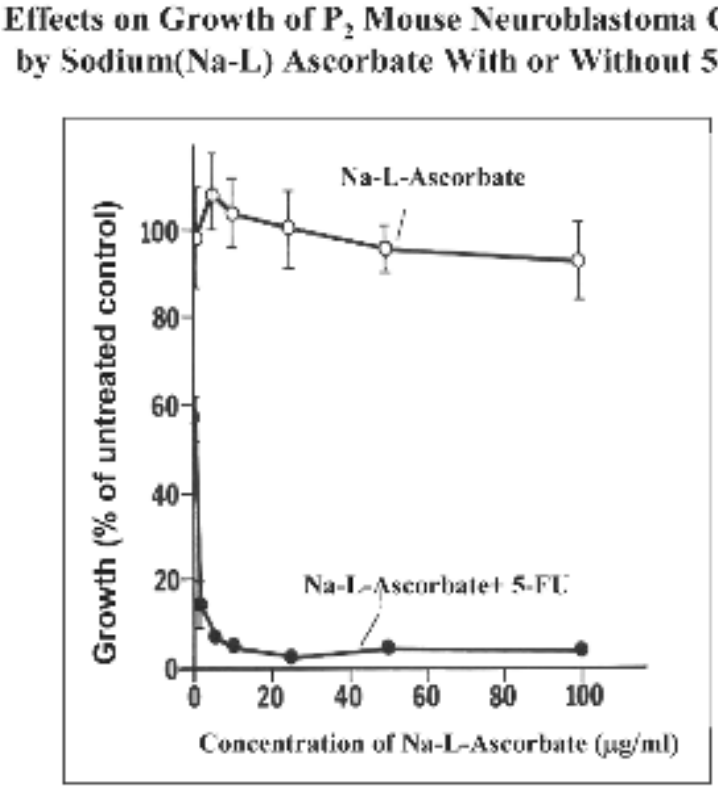


Figure 2: Neuroblastoma cells were plated in tissue culture dishes (60 mm), and 5-fluorouracil (5-FU, 0.08 μg/ml together with various concentration of sodium ascorbate were added 24 hours after plating. Fresh medium, 5-FU, and sodium ascorbate changed 2 days after treatment and cells were counted 3 days after treatment. The number of cells in treated groups was expressed as % of untreated controls). Each value is the average of 6-9 samples + Standard deviation (7).

Vitamin E Succinate

A d-alpha-tocopheryl succinate (vitamin E succinate) at therapeutic doses before irradiation enhanced the cytotoxic effects of gamma-irradiation on murine neuroblastoma cells in culture (45) (Figure 3). Treatment with vitamin E succinate induced chromosomal damage in human cervical cancer cells and ovarian cancer cells, but not in human normal fibroblasts in culture. In addition, administration of vitamin E succinate enhanced the levels of radiation-induced chromosomal damage in cancer cells, but it reduced chromosomal damage in normal cells (46, 47) (Figure 4). Vitamin E succinate at therapeutic doses enhanced the cytotoxic effects of Adriamycin on human prostate cancer cells in culture (48). Vitamin E succinate also enhanced the toxicity of Adriamycin on human cervical cancer cells (HeLa cells) but not on human normal fibroblasts (49) (Table 3).

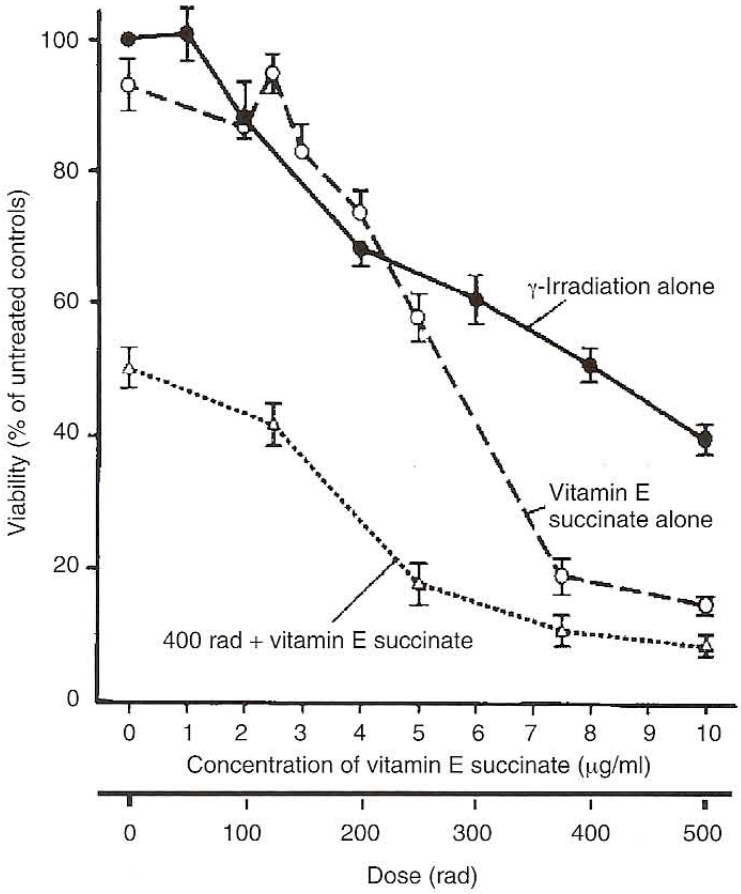


Figure 3: Neuroblastoma cells (NBP2) were gamma-irradiated 24 after plating in tissue culture dishes. Vitamin E suucinate or solvent was added immediately before irradiation. Fresh growth medium, vitamin E succinct, and solvent were changed 2 days after irradiation. Cells were counted 3 days later. The number of cells in treated groups was expressed as % of untreated controls. Each experiment was repeated at least twice involving 3 samples per experiment. The bar at each point is SEM (45)

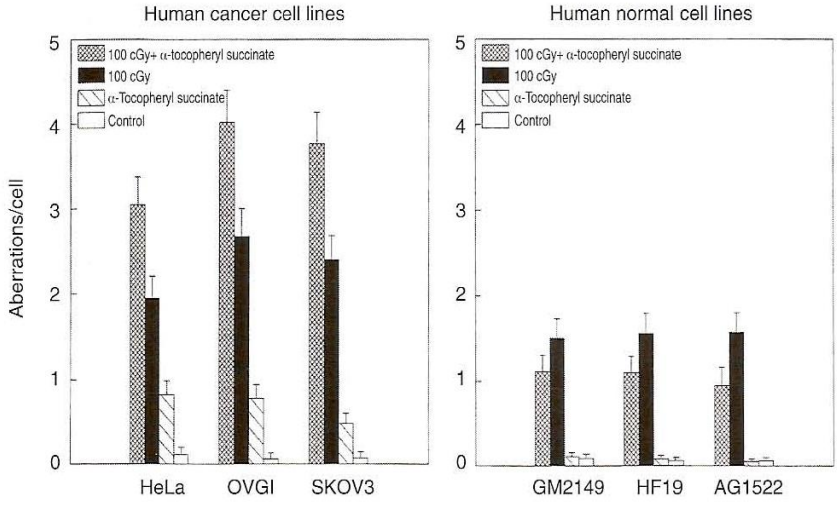


Figure 4: Effect of alpha-tocopheryl succinate on the level of gamma- radiation-induced chromosomal damage in human cervical cancer (HeLa cells), ovarian carcinoma cell line (OVG1

URL: http://doi.org/10.14738/abr.124.16842

and SKOV3) and human normal fibroblasts (GM2149), HF19, and AG1522). Alpha-tocopheryl succinate treatment increased chromosomal damage as well enhanced radiation-induced chromosomal damage in all 3 cancer cell lines but not in normal cell line (46, 47).

Table 3: Enhancement of the Effect of Certain Chemotherapeutic Agents by a Mixture of Four Antioxidants on Human Melanoma Cells in Culture

Treatments	Cell Number (% of Controls)
Solvent	101 ± 4[a]
Cis-platin (1 μg/ml)	67 ± 4
Antioxidant mixture	56 ± 3
Cisplatin + Antioxidant mixture	38 ± 2
Tamoxifen (2 μg/ml)	81 ± 3
Tamoxifen + Antioxidant mixture	30 ± 2
DTIC (100 μg/ml)	71 ± 2
DTIC + Antioxidant mixture	38 ± 2

Data were summarized from a previous publication (49)., a = standard error of the mean**,** Vitamin C, 50 μg/ml; polar carotenoids, 10 μg/ml; alpha-tocopheryl succinate, 10 μg/ml and 13-cis-retinoic acid, 7.5 μg/ml were added simultaneously with chemotherapeutic agents**.,** DTIC = 5-(3,3-Dimethyl-1-triazeno) imidazole-4-carboxamide

Resveratrol

Treatment with resveratrol at a therapeutic dose before irradiation increased apoptosis in breast cancer cells in culture (MCF-7). Thus, resveratrol acts as a radio-sensitizing agent for breast cancer cells (50). Resveratrol treatment reduced cell proliferation and cell cycle arrest in S phase in a dose-dependent manner in NK/T cell lymphoma (NKTCL) derived from a highly aggressive non-Hodgkin lymphoma with poor diagnosis (51). This study also revealed that resveratrol in combination with ionizing radiation induced apoptosis in cancer cells. Resveratrol at therapeutic doses inhibited the growth of androgen-sensitive (22RV1) and androgen insensitive prostate cancer cells but not of normal prostate epithelial cells. This treatment also enhanced the effects of ionizing radiation-induced on apoptosis, cell cycle arrest at G1-S phase of the cell cycle, and double-strand DNA breaks in prostate cancer cells (52).

Curcumin

Treatment with curcumin before x-irradiation enhanced the levels of apoptosis in radioresistant cervical cancer cells (53). Curcumin treatment also increased the cell killing effect of arsenic oxide on multiple myeloma cells in culture (U266 cell line) (54). Curcumin enhanced lonidamine-induced apoptosis in cancer cells (55). Curcumin increased the effectiveness of chemotherapy and radiation therapy on cancer cells while reducing damage to the normal tissues leading to increased survival time (56)

Antioxidant Mixture

A mixture of retinoic acid, vitamin C, vitamin E succinate, and polar carotenoids reduced the growth of human melanoma cells (SK-30) in culture, and enhanced the cytotoxic effects of tamoxifen, cisplatin, and DTIC (57) (Table 4).

Table 4: Modification of Adriamycin Effect on Human Cervical Cancer Cells (HeLa) and Human Normal Skin Fibroblasts in Culture by d-α-Tocopheryl Succinate

Treatment	HeLa Cells	Normal fibroblasts
Solvent Control	99 ± 2.6*	104 ± 3.4
Adriamycin (0.1 µg/ml)	57 ± 6.2	77 ± 2.4
α-TS (10 µg/ml)	99 ± 1.6	101 ± 3.7
Adriamycin (0.1 µg/ml) Plusα-TS	20 ± 7.9	77 ± 1.7
Adriamycin (0.25 µg/ml)	14 ± 2.9	68 ± 1.0
Adriamycin (0.25 µg/ml) Plus α-TS	5 ± 0.8	62 ± 1.8

Cells (20,000) were plated in 24-well chamber and Adriamycin and α-tocopheryl succinate (α-TS) were added one after another at the same time. Drug, α-TS, and fresh growth medium were changed at 2 days after treatment and the viability of cells was determined by MTT assay. Growth in experimental groups was expressed % of untreated control. Each experiment was repeated at least twice, and each value represents an average of 6-9 samples ± SEM (57).

GLUCOSE AND GLUTAMINE ARE REQUIRED FOR THE SURVIVAL AND GROWTH OF CANCER CELLS

Several studies and reviews have suggested that glucose and glutamine metabolism are required for the survival and growth of cancer cells (58-60). Glucose and glutamine are most abundant nutrients in the plasma. Glucose is primarily needed to produce energy, while glutamine is utilized to make several molecules to maintain survival and growth of cancer cells. some studies supporting nutrient requirements for the survival and growth of cancer cells are described here.

Glucose

All cancer cells require glucose to generate energy which is needed for their survival and growth. Cancer cells utilize an inefficient energy-producing system, glycolysis, which converts one molecule of glucose to 2 molecules of ATP (adenosine triphosphate), whereas normal cells use oxidative phosphorylation pathways which generate 36 ATP from one molecule of glucose. Cancer cells show an increased expression of glucose transporters GLUT-1 and GLUT-3 that enhance the uptake of glucose causing increased accumulation of glucose in these cells. Excess glucose is oxidized to produce extensive amounts free radicals which are required for the proliferation and metastasis of cancer cells (3). In addition, increased accumulation of glucose leads to more production of lactic acid making cellular environment acidic which favors growth of cancer cells (61). Inhibitors of glucose transporters GLUT-1 and GLUT-3 increase the death of cancer cell by inhibiting the uptake of glucose (62).

Glutamine

Glutamine uptake and metabolism are required for the survival and growth of cancer cells (63). A few reviews have described the function of glutamine in cancer cells (58). It provides source of energy, and nitrogen for protein and nucleic acid synthesis that are essential for the survival and proliferation of tumor cells (64). Therefore, preventing the uptake of glutamine may cause death of cancer cells (65, 66). In addition, glutamine also plays a central role in inducing resistance to chemotherapy and radiation therapy, because it promotes the synthesis of glutathione which protects cancer cells from oxidative damage, and thereby, allowing

URL: http://doi.org/10.14738/abr.124.16842

progression of cancer cells (67). In addition, increased expression of glutamine synthetase which enhances the levels of glutamine in cancer cells causes them to become resistance to radiation therapy for the same reasons (68). Conversely, inhibition of glutamine synthetase in cancer cells can lead to their death (69). It has been demonstrated that reducing the availability of glutamine promotes radiosensitivity (70). It has been shown that inhibition of glutamine metabolism increases the sensitivity of Kras positive pancreatic ductal adenocarcinoma to radiation therapy (71). These studies suggest that inhibition of uptake or metabolism of glutamine would cause death of tumor cells.

EFFECTS OF THERAPEUTIC DOSES OF INDIVIDUAL ANTIOXIDANTS ON INHIBITION OF GLUCOSE UPTAKE AND METABOLISM IN CANCER CELLS

Vitamin C

Administration of therapeutic dose of vitamin C inhibited glycolysis by inactivating glyceraldehyde 3-phosphate dehydrogenase (GAPDH) which participates in producing ATP, and thus creates energy crisis (72) causing death of human colorectal cancer (CRC cell line) carrying Kras mutation or Braf mutation which makes them resistance to standard therapies (73). vitamin C-induced inactivation of this enzyme would create energy crisis in the tumor cells leading to cell death. Treatment with therapeutic doses vitamin C inhibited glycolysis, creating an energy crisis in the tumor cells leading to cell death (44, 74, 75).

Alpha-lipoic Acid

Administration of alpha-lipoic acid at therapeutic doses reduced glucose uptake and reduced the growth of neuroblastoma cells and breast cancer cells (SKBr3 cell line) in culture and transplanted in a thymic mouse (76).

Quercetin and Epigallocatechin Gallate (EGCG)

Administration of quercetin blocked the uptake of glucose leading to inhibition of glycolysis causing growth inhibition of tumor cells in culture and reduced growth and metastasis in animal model by decreasing the levels of its marker matrix metalloproteinase 2 (MMP-2), MMP-9, and vascular endothelial growth factor (VEGF). This study revealed that quercetin also inhibited tumor growth and metastasis by inhibiting glycolysis in vivo (77). Quercetin treatment also reduced glucose uptake in estrogen receptor-positive (MCF-7) and estrogen receptor-negative (MDA-MB-231) breast cancer cells in culture (78, 79). Both quercetin and EGCG inhibited the uptake of glucose and reduced the growth of estrogen receptor (ER)-positive (MCF7) and ER-negative MDA-MB-231 breast cancer cells in culture (80).

Resveratrol

Administration of resveratrol-loaded polymeric nanoparticles reduced glucose metabolism and inhibited the growth of colon cancer cells in culture (CT26 cell line) and in CT26 transplanted mice (81). Resveratrol induced apoptosis in ovarian cancer cells in culture by inhibiting the uptake of glucose (82, 83). Treatment with resveratrol reduced glucose uptake and glycolysis in breast cancer cells in culture and reduced the growth of tumor in mice carrying Lewis Lung carcinoma, HT-colon cancer, and breast cancer cells (T47D) (84).

Curcumin

Treatment with curcumin treatment inhibited glucose uptake in varieties of cancer cells and reduced their growth (85). It also prevented high glucose-induced chemoresistance by blocking the uptake of glucose (86).

EFFECTS OF THERAPEUTIC DOSES OF ANTIOXIDANTS ON INHIBITION OF UPTAKE AND METABOLISM OF GLUTAMINE ON CANCER CELLS

Resveratrol

Resveratrol and cisplatin treatment individually enhanced the levels of phosphorylated H2AX (yH2AX), a marker of DNA double-strand breaks (DSBs), in hepatoma cells in culture, and the combination of two produced more pronounced increase in DNA (DSBs) levels. Resveratrol treatment inhibited glutamine metabolism, which may account for the enhancement of growth inhibitory effects of cisplatin on hepatoma cells (87).

Omega-3-fatty Acids in Combination with Rapamycin

Treatment of breast cancer cells in culture or in transplanted mice carrying tumor cells with omega-3 inhibited glucose and glutamine metabolism and reduced their growth. The combination of omega-3-fatty acids and rapamycin produced synergistic effects on cell cycle arrest and apoptosis and more pronounced inhibition in glutamine metabolism (88).

Curcumin in Combination with Cisplatin

Curcumin treatment in combination with cisplatin suppressed proliferation of colon cancer cells in a synergistic manner. In addition, curcumin treatment overcame cisplatin resistance colon cancer cells by inhibiting the uptake of glutamine (89).

Vitamin D3

Treatment with vitamin D3 at a therapeutic dose inhibited glutamine uptake and reduced the growth of H-ras transformed human breast epithelial cells. This effect of vitamin D3 was mediated by reducing the level of a major glutamine transporter protein (SLC1A5). Vitamin D3 treatment inhibited glutamine uptake and reduced the growth of human breast cancer in culture (90).

THERAPEUTIC DOSES OF ANTIOXIDANTS KILL THERAPY RESISTANT CANCER CELLS BY BYPASSING PROTECTIVE EFFECTS OF HIGH EXPRESSION OF NRF2 AND GLUTATHIONE PEROXIDASE

Nrf2, a nuclear transcriptional factor, is constitutively expressed in cancer cells (91). Activation of Nrf2 increases the level of antioxidant enzymes, which protect cancer cells from oxidative damage, allowing rapid progression and metastasis, and making them resistant to therapeutic agents. In addition, Glutathione peroxidase-2, which is highly expressed in cancer cells (92), produces enhanced level of glutathione that protects cancer cells from oxidative damage and make them resistant to therapeutic agents. Therapeutic doses of antioxidants bypass the effect of these protective mechanisms and kill cancer cells by blocking the uptake and metabolism of glucose and glutamine.

URL: http://doi.org/10.14738/abr.124.16842

PROPOSED HYPOTHESIS FOR USING A MIXTURE OF THERAPEUTIC DOSES OF MULTIPLE ANTIOXIDANTS ALONE OR IN COMBINATION WITH CHEMOTHERAPY AND RADIATION THERAPY TO IMPROVE TREATMENT OF CANCER

Based on the studies presented in this manuscript, we propose that therapeutic doses of a mixture of micronutrients containing multiple antioxidants may reduce tumor growth by blocking uptake and metabolism of glucose and glutamine without affecting the growth of normal cells. This mixture contains therapeutic doses of vitamin A, vitamin C, vitamin D3, vitamin E succinate, R-α-lipoic acid, N-acetylcysteine, coenzyme Q10, curcumin, resveratrol, quercetin, and natural beta-carotene. In addition, this mixture contains all B-vitamins, and minerals selenium and zinc at the preventive doses. The proposed micronutrient mixture in combination with a standard may enhance their effectiveness in reducing tumor growth more than produced by either agent alone, while causing no significant damage to normal cells. Pre-clinical and clinical studies with the proposed mixture of therapeutic doses of antioxidants should be performed to test the validity of proposed hypothesis in improving the treatment of cancer.

CONCLUSIONS

Although chemotherapy and radiation therapy improve 5-year survival rate in majority of cancers, the acute toxicity during treatment and late adverse effects of therapies remain a major concern of oncologists. To further improve 5-year survival rate and reduce adverse effects of therapies, a new non-toxic approach is proposed. This approach suggests that therapeutic doses of antioxidants inhibit the growth of cancer cells and enhance the growth-inhibitory effects of chemotherapy and radiation therapy on cancer cells but not on normal cells. Cancer cells require glucose and glutamine for their survival and growth. We have proposed that selectivity of therapeutic doses of antioxidants in killing cancer cells, but not normal cells may be due to inhibition of the uptake and metabolism of glucoses and glutamine. This hypothesis is supported by several experimental studies which show that therapeutic doses of antioxidants inhibit the uptake and metabolism of glucose and glutamine. Excessive amounts of free radicals are required for the rapid growth and metastasis of cancer cells but are protected from oxidative damage because of high expression of Nrf2 which increases the levels of antioxidant enzymes and glutathione peroxidase which increases the levels of glutathione. However, therapeutic doses of antioxidants bypass these protective mechanisms by preventing the uptake and metabolism of glucose and glutamine. Therefore, therapeutic doses of antioxidants may reduce the rate of proliferation and the risk of metastasis. We have proposed that oral administration of a mixture of micronutrients containing therapeutic doses of multiple antioxidants alone or in combination with chemotherapy or radiation therapy may improve the survival time more than that produced by individual therapy and reduce acute and late adverse effects of therapies. The validity of the proposed hypothesis for improving treatment of cancer should be tested by pre-clinical and clinical studies.

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