World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 7.409

LIMITATIONS OF CANCER TREATMENT WITH CHEMOTHERAPY AND RADIATION THERAPY AND PROPOSED PLAN TO IMPROVE THEM

Kedar N. Prasad* PhD,

Engage Global Inc, 245 El Faisan Drive, San Rafael, California 94903, USA.

***Corresponding Author: Kedar N. Prasad* PhD**

PhD, Engage Global Inc, 245 El Faisan Drive, San Rafael, California 94903, USA.

Article Received on 01/08/2024 **Article Revised on 21/08/2024** **Article Accepted on 11/09/2024**

ABSTRACT

Widely used chemotherapy and radiation therapy have produced increased 5-year survival rate for most of the cancer. However, acute toxicity during treatment and enhanced risk of late adverse effects such as neoplastic and non-neoplastic diseases exist. To improve survival rate further and reduce acute and late adverse effects of these therapies a novel a novel radiation delivery technology called FLASH radiation therapy (FLASH-RT) which can irradiate tumor and normal tissues *in vivo* at an ultra-dose rate of 40 Gy/s or more compared to conventional radiation therapy dose rate of 0.01 Gy/s or more was developed. Although FLASH-RT protected normal tissue, but the tumor response was like conventional radiation therapy. Tumors irrespective of their type or sensitivity to chemotherapy and radiation therapy require the uptake and metabolism of glucose and glutamine for survival and growth. To improve tumor response rate and reduce both acute and late adverse effects of chemotherapy and radiation therapy, we propose that supplementation with a micronutrient mixture containing high doses of multiple antioxidants which would kill cancer cells but not normal cells by inhibiting the uptake and metabolism of glucose and glutamine. This micronutrient mixture would also enhance the growth-inhibitory effects of chemotherapy and radiation therapy on cancer cells, while protecting acute and late adverse effects of these therapies. Intestinal dysbiosis promotes the development of cancers and reduces the effectiveness of chemotherapy and radiation therapy and enhances their acute toxicities. Therefore, we also propose that supplementation with probiotics with prebiotics which would reverse the effects of intestinal dysbiosis and improve the effectiveness of chemotherapy and radiation therapy.

KEYWORDS: Cancer; High dose antioxidants; Glucose; Glutamine; Intestinal dysbiosis; Probiotics with

1. INTRODUCTION

Although widely used chemotherapy and radiation therapy have increased 5-year survival rate for most tumors, serious limitations of these therapies exist. Damage to the normal tissue during and after treatment remains the major concerns of oncologists. The acute side-effects during cancer treatment such as diarrhea, vomiting, and fatigue occur. The late adverse effects of treatment among cancer survivors include neoplastic and non-neoplastic diseases. In addition, increased annual death from this disease occurs among cancer patients. To improve the efficacy of chemotherapy and radiation therapy, a new approach which can increase 5-year survival rate for all tumors and reduce their acute and late adverse effects is needed.

This review briefly presents a novel radiation delivery technology called FLASH-radiation therapy (FLASH-RT) which delivers dose at an ultra-dose rate, which protects normal tissue, but no change in tumor response rate compared to conventional radiation therapy. This review describes evidence which show that supplementation with a micronutrient mixture containing high doses of multiple antioxidants which would kill cancer cells but not normal cells and enhances the growth-inhibitory effects of radiation and chemotherapy on cancer cells while protecting normal cells. This review describes evidence to show that supplementation with probiotics with prebiotics would reverse harmful effects of intestinal dysbiosis during chemotherapy and radiation therapy, and thereby improve the effectiveness of these therapies.

2. Development of FLASH Radiation Therapy

In 2014, a novel radiation delivery technology called FLASH radiation therapy (FLASH-RT) which can irradiate tumor and normal tissues *in vivo* at an ultra-dose rate of 40 Gy/s or more compared to conventional radiation therapy dose rate of 0.01 Gy/s or more was developed. FLASH-RT produces transient hypoxia in

both tumor and normal cells. Using lung cancer transplanted athymic mice as an experimental model, it was demonstrated that both FLASH-RT and conventional radiation therapy reduced the growth of tumor to the same extent, but conventional radiation therapy caused lung fibrosis and acute apoptotic cell death of muscle and epithelial cells, whereas FLASH-RT did not.[1] Pre-clinical studies on mice, mini pig, and cat further confirmed the advantage of FLASH-RT over conventional radiation therapy in protecting normal tissues including the brain,[2,5] the skin,[6] and the blood.[7] The first clinical study with FLASH-RT was conducted on 75-year-old patients with multi-resistance CD30+ T cell cutaneous lymphoma metastasized throughout the whole skin surface. Results showed that FLASH-RT reduced tumor growth to the same extent as conventional radiation therapy while protecting the skin.[8] FLASH-RT protects normal tissue during therapy, while conventional radiation therapy did not. Since FLASH-RT produces tumor response rate like conventional radiation therapy, additional new approach which enhance radiation therapy-induced tumor response rate and reduce acute and late adverse effects of radiation therapy is needed.

3. Proposed use of high doses of individual antioxidant which inhibits the growth of cancer cells but not of normal cells

3.1. Vitamin C (As sodium ascorbate: In 1976, Dr. Linus Pauling and his colleagues were first to demonstrate that vitamin C at high doses inhibited the growth of cancer cells without affecting the growth of normal cells in cancer patients.[9,10] This observation became controversial because others could not confirm their observation. However, we confirmed their work by showing that vitamin C at high doses killed all murine neuroblastoma (NB) cells in culture; however, the growth of normal fibroblasts in culture was only slightly reduced. This study also demonstrated that glioma cells in culture were relatively less sensitive to vitamin C than neuroblastoma cell.[11] Vitamin C at high doses inhibited the growth of human tumorigenic parotid acinar cells in culture but had no effect on the growth of non-tumorigenic parotid acinar cells.[12] This study also showed that vitamin C at low doses stimulated the growth of tumorigenic parotid acinar cells in culture.

3.2. D-alpha-tocopheryl succinate (Vitamin E succinate): In 1982, we discovered that vitamin E succinate at high doses induced differentiation and growth inhibition in murine melanoma cells in culture[13] (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.[14] Several studies using other cancer cell lines in culture and in animal models of cancer confirmed growth-inhibitory effects of vitamin E succinate.[15,19] A recent review has further documented the role of vitamin E succinate in inhibiting the growth of tumor cells.[20]

3.3. Beta-carotene and Retinol: Beta-carotene and retinol treatment at high doses induced differentiation in murine NB cells and B-16 murine melanoma cells in culture, respectively, and inhibited their growth.[21]

3.4. Quercetin: Overexpression of cyclooxygenase (COX-2) plays a significant role in the development and progression of cancer. Treatment with high doses of quercetin induced apoptosis and inhibited the growth of human colon cancer cells (HT29 cells) over-expressing Cox-2 enzyme, but it was less effective in human colon cancer (HCT 15 cell line) expressing reduced level of COX-2 enzyme and had a minimal effect on normal epithelial cell line (IEC-6).[22]

3.5. Resveratrol: Treatment with high doses of resveratrol reduced the growth of human leiomyoma cells in culture and in rat-derived uterine leiomyoma transplanted in athymic mice.[23]

3.6. Coenzyme Q10: The effectiveness of coenzyme Q10 on human cancer remains controversial. A few clinical studies showed that daily supplementation of coenzyme Q10 at high doses of 390 mg or more may increase the survival of breast cancer patients receiving standard cancer therapy.[24,26] On the other hand, another clinical study on breast cancer revealed that supplementation with 300 mg coenzyme Q10 did not improve the extent of fatigue or the quality of life.[27]

3.7. Curcumin: A few reviews and studies have shown that treatment with high doses of curcumin inhibits the growth and induces apoptosis in various cancer cells in culture.[28,29] Curcumin treatment markedly reduced the growth of gastric carcinoma and suppressed gastric-mediated secretion, which inhibited the progression of gastric cancer cells[30] Curcumin treatment also reduced proliferation of human colon cancer cells in culture.[31]

4. Multiple antioxidants inhibited the growth of cancer cells but not of normal cells

A micronutrient mixture containing quercetin, curcumin, resveratrol, green tea extract, and cruciferex inhibited the growth of human Faconi anemia head and neck squamous cell carcinoma in culture (OHSU-974 cell line), in athymic mice, and in fibrosarcoma (HT-180 cell line) and melanoma (A2058 cell line) in culture.[32] 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.[33]

5. High doses of individual antioxidants in combination with Radiation and Chemotherapeutic agents

5.1. Vitamin C: As early as in 1979, it was demonstrated that high doses of vitamin C as sodium ascorbate enhanced the growth-inhibitory effects of x-radiation and certain chemotherapeutic agents on neuroblastoma cells in culture.[11] For example, vitamin C enhanced the growth-inhibitory-effect of 5-FU (5-Fluorouracil) in neuroblastoma cells in culture (Figure 2). Since then, several studies using other antioxidants and their analogs and different cancer cells have established the general relevance of the above observation.

Intravenous administration of high doses of vitamin C in combination with gemcitabine and radiation therapy increased overall survival time in patients with pancreatic cancer compared to individual agent. This study also demonstrated that high doses of vitamin C sensitize the effect of radiation on pancreatic cancer cells but inhibited radiation-induced damage to normal cells.[34,35]

5.2. Vitamin E: Administration of **d**-alpha-tocopheryl succinate (vitamin E succinate) at high doses before irradiation enhanced the cytotoxic effects of gamma-irradiation on murine neuroblastoma cells in culture.[36] (Figure 3). 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, vitamin E succinate enhanced the levels of radiation-induced chromosomal damage in cancer cells, but it reduced damage to normal cells.[37,38] (Figure 4). Vitamin E succinate at high doses enhanced the cytotoxic effects of Adriamycin on human prostate cancer cells in culture.[39] Vitamin E succinate also enhanced the toxicity of Adriamycin on human cervical cancer cells (HeLa cells) but not on human normal fibroblasts[40] (Table 1).

5.3. Vitamin A and Beta-carotene: Administration of vitamin A and beta-carotene produced one-year survival in x-irradiated mice with transplanted adenocarcinoma compared to no survival in x-irradiated controls.[41] Beta carotene reduced radiation-induced oral mucositis without interfering with the efficacy of radiation therapy in patients with head and neck cancer.[42]

5.4. Resveratrol: In breast cancer cells in culture (MCF-7), treatment with high doses of resveratrol before irradiation increased apoptosis. Thus, resveratrol acts as a radio- sensitizing agent in breast cancer cells.[43] In NK/T cell lymphoma (NKTCL) derived from a highly aggressive non-Hodgkin lymphoma with poor diagnosis, resveratrol treatment reduced cell proliferation and cell cycle arrest in S phase in a dose-dependent manner.[44] This study also showed that high doses of resveratrol enhanced radiation induced apoptosis in cancer cells. Resveratrol at high 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 radiation-induced apoptosis, -cell cycle arrest at G1-S phase of the cell cycle, and -double-strand DNA breaks on prostate cancer cells.[45]

5.5. Curcumin: Pre-treatment with curcumin enhanced the levels of radiation-induced apoptosis in radioresistant cervical cancer cells.[46] Curcumin treatment enhanced the cell killing effect of arsenic oxide in on multiple myeloma cells in culture (U266 cell line).[47] High doses of curcumin enhanced lonidamine-induced apoptosis in cancer cells.[46] Curcumin increases the effectiveness of chemotherapy and radiation therapy on cancer cells while reducing damage to the normal tissues leading to increased survival time.[49]

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.[50]

During last 40 years, several articles and reviews have been published to show that high doses of individual antioxidants inhibited the growth of tumor cells and enhanced the growth-inhibitory of chemotherapy and radiation therapy on cancer cells without significantly affecting the growth of normal cells in experimental models such as cell culture models and in athymic mice carrying transplanted tumor cells. However, these exciting observations to improve the current treatment of tumor have not drawn any attention from the oncologists. One of the main reasons could be that oncologists fear that antioxidants may block the growth-inhibitory effect of chemotherapy and radiation therapy on cancer cells which is mediated by free radicals. Since antioxidants are known to scavenge free radicals, the fear of oncologists was justified. Furthermore, vitamin C at preventive doses (low doses) stimulated the growth of cancer cells (6) which further discouraged the use of antioxidants in the management of cancer. The difference between the mechanisms of action between low and high doses of antioxidant was not available at that time.

While searching for the mechanisms of action of high doses of antioxidants, the question arose, do cancer cells require specific nutrients for survival and growth?. The search for studies on this issue revealed that all cancer cells irrespective of type and sensitivity to tumor therapeutic agents require glucose and glutamine for their survival and growth.

6. Cancer cells require Glucose and Glutamine for the Survival and Growth

Several studies and reviews have suggested that glucose and glutamine metabolism are required for the survival and growth of cancer cells.[51,53] Glucose and glutamine are most abundant nutrients in the plasma. Glucose is primarily needed to activate bioenergetic pathways, while glutamine is utilized to activate biosynthetic pathways to maintain survival and growth of neoplastic cells. The studies supporting the requirements of these nutrients for the survival and growth of cancer cells are described here.

6.1. Glucose: Glucose is required to generate energy which is needed for the survival and growth of normal and cancer cells. However, glucose metabolism to generate energy in cancer cells is different from that in normal cells. For example, cancer cells utilize an inefficient energy-producing system, glycolysis, which converts one molecule of glucose to 2 molecules of ATP (adenosine triphosphate). This amount of energy is not enough for maintaining the survival and growth of cancer cells; therefore, they consume glucose at a much higher rate to generate sufficient energy for their survival and growth. This is in contrast to normal cells which utilize oxidative phosphorylation pathways, which generate 36 ATP from one molecule of glucose. Thus, normal cells do not require as much glucose as cancer cells to meet their energy requirements. Cancer cells exhibit upregulation of glucose transporters GLUT-1 and GLUT-3 that increase the uptake of glucose. Inhibition of glucose transporters may increase the death of cancer cell by inhibiting the uptake of glucose.[54]

6.2. Glutamine: Glutamine metabolism is essential for the survival and growth of neoplastic cells.[55] A few reviews have described the function of glutamine in cancer cells.[51] It provides source of energy and nitrogen for protein and nucleic acid synthesis. Glutamine is converted to glutamate by glutaminase 1(GLS1) and then glutamate is converted to alpha-ketoglutarate, which enters the TCA (tricarboxylic acid) cycle for generating energy. Glutamine is also used for synthesizing several vital molecules that are essential for the survival and proliferation of tumor cells.[56] Deprivation of glutamine may cause death of cancer cells.[57,58] In addition, glutamine promotes synthesis of glutathione which can protect cancer cells from oxidative damage, and thereby, participates in their resistance to standard tumor therapy and their progression.[59] In addition, increased expression of glutamine synthetase which enhances the levels of glutamine in cancer cells causes them to become resistance to radiation therapy because of enhanced DNA repair ability.[60] Conversely, inhibition of glutamine synthetase in cancer cells can lead to death of cancer cells.[61] Reducing the availability of glutamine promotes radiosensitivity.[62] Therefore, inhibition of uptake or metabolism of glutamine would cause death of tumor cells. it has been shown that inhibition of glutamine metabolism enhances the sensitivity of Kras positive pancreatic ductal adenocarcinoma to radiation therapy.[63]

7. High Doses of Individual Antioxidants Inhibit Uptake and Metabolism of Glucose in Cancer Cells

We propose that high doses of antioxidants may block the uptake and metabolism of glucose and glutamine in cancer cells leading to their death without affecting the growth of normal cells. High doses of individual antioxidant enhance the growth-inhibitory effects of chemotherapeutic agents on cancer cells, but not on normal cells by the same mechanism. Effects of high doses of individual antioxidant showing the inhibition of glucose uptake and metabolism are described here.

7.1. High doses of vitamin C: Administration of high doses of vitamin C killed selectively human colorectal cancer (CRC cell line) carrying Kras mutation or Braf mutation which make them resistant to standard therapies by inhibiting glycolysis.[64] In human colorectal cancer cells, which had become resistance to standard cancer therapies, treatment with high doses of vitamin C inhibited glycolysis, creating an energy crisis in the tumor cells leading to their death.[35,65,66]

7.2. High doses of alpha-lipoic acid: Administration of alpha-lipoic acid at high doses reduced glucose uptake and inhibited the growth of neuroblastoma cells and breast cancer cells (SKBr3 cell line) in culture and transplanted in a thymic mouse.[67]

7.3. High Doses of 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 also showed that quercetin also inhibited tumor growth and metastasis by inhibiting glycolysis in vivo.[68] Quercetin treatment also reduced glucose uptake in estrogen receptor-positive (MCF-7) and estrogen receptor-negative (MDA-MB-231) breast cancer cells in culture.[69,70] 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.[71]

7.4. High doses of 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.[72] Resveratrol induced apoptosis in ovarian cancer cells in culture by inhibiting the uptake of glucose.[73,74] 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).[75]

7.5. High doses of curcumin: Treatment with high doses of curcumin inhibited glucose uptake and lactate production in varieties of cancer cells and reduced their growth.[76] It also prevented high glucose-induced chemoresistance by blocking the uptake of glucose.[77]

8. High Doses of Antioxidants Inhibit Uptake and Metabolism of Glutamine in Cancer Cells

8.1. High doses of 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). Resveratrol treatment inhibited glutamine metabolism, which may account for the enhancement of growth inhibitory effects of cisplatin on hepatoma cells.[78]

8.2. High doses of Omega-3 in combination with rapamycin: Treatment of breast cancer cells in culture or in transplanted mice carrying tumor cells with omega 3 inhibited glutamine metabolism and reduced their growth. The combination of omega-3 and rapamycin produced synergistic effects on cell cycle arrest, apoptosis, and more pronounced inhibition in glutamine metabolism.[79]

8.3. High doses of 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.[80]

8.4. High doses of Vitamin D3: Treatment of H-ras transformed human breast epithelial cells with vitamin D3 inhibited glutamine uptake and reduced their growth. Vitamin D3 treatment inhibited glutamine uptake and reduced the growth of human breast cancer in culture.[81]

9. Tumor response to increased production of Reactive oxygen species (ROS)

The production of ROS is elevated in cancer cells because of high metabolic rate, gene mutation, and partial hypoxia.[82] To meet this challenge, tumor cells acquire antioxidant activity to protect themselves from oxidative damage.[83] This is further evidenced by the observation that when tumor cells become resistant to chemotherapy and radiation therapy, they increase the levels of glutathione which allows cancer cells to grow rapidly and metastasis in the presence of high levels of ROS.

10. High Doses of Antioxidants kill Cancer Cells by bypassing the Protective Antioxidants

Nrf2, a nuclear transcriptional factor, is constitutively expressed in cancer cells.[84] 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 current therapeutic agents. In addition, Glutathione peroxidase - 2, which is highly expressed in cancer cells,[85] produces enhanced level of glutathione that protects cancer cells from oxidative damage and make them resistant to chemotherapy and radiation therapy. High doses of antioxidants kill cancer cells by bypassing the above protective mechanisms by blocking glucose uptake and inhibiting glutamine metabolism.

11. Proposed Micronutrient Mixture Containing High Doses of Multiple Antioxidants Alone or in Combination with Chemotherapy and Radiation Therapy in the Treatment of Cancer

Based on the studies presented in this manuscript, we propose that a micronutrient mixture containing high doses of 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 high doses of vitamin A as retinal palmitate, vitamin C as sodium ascorbate, vitamin D3, vitamin E succinate, R-α-lipoic acid, N-acetylcysteine, coenzyme Q10, curcumin, resveratrol, 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 chemotherapy and radiation therapy may enhance their effectiveness in reducing tumor growth more than produced by either agent alone, while causing no significant damage to normal cells. This micronutrient mixture has been patented (patent number 11,938,152). Clinical studies with the proposed micronutrient mixture containing high doses of antioxidants should be performed to test the validity of suggested hypothesis for improving the effectiveness of chemotherapy and radiation therapy and reducing their acute and late adverse effects.

12. Intestinal dysbiosis in Initiation and Progression of cancer cells

Recent studies suggest that intestinal dysbiosis in which the composition of bacterial population changes in favor of toxic bacteria plays an important role in the initiation and progression of cancer, and the effectiveness chemotherapy and radiation therapy. In addition, it enhances chemotherapy- and radiation therapy-induced acute adverse effects during treatment and reduces effectiveness of these therapies. Intestinal dysbiosis is closely associated with the increased incidence of several types of cancer including, colorectal cancer, lung cancer,

esophageal cancer, gastric cancer, hepatobiliary cancer, and pancreatic cancer.[86] The growth of harmful bacteria generates several harmful chemicals including proinflammatory cytokines which are toxic to the cells. The intestinal dysbiosis decreases the production of short-chain fatty acids such as butyric acid, propionic acid, and acetic acid. Butyric acid has diverse biological functions which include improving intestinal barrier integrity.[87] and acting as an anti-cancer agent.[88] Intestinal dysbiosis also causes inflammation and enhances the intestinal permeability.

12.1. Intestinal dysbiosis in progression of colorectal cancer (CRC): Despite current treatments, approximately 50% of the patients develop incurable recurring CRC.[89] The exact reasons are not known; however, growing evidence suggest that chemotherapy and radiation therapy can enhance the levels of already existing intestinal dysbiosis that can interfere with the effectiveness of their treatment and eventually making cancer resistant to therapy. The presence of toxic bacteria *Fusobacterium nucleatum* has been demonstrated in CRC (90-91). These pathogenic bacteria promote progression of CRC and is associated with poor prognosis and drug resistance.[90] Another toxic bacterium *Bacteroides fragilis* which is present in the gut secretes toxins that can destroy epithelial barrier in the gut, induce inflammation and precancerous lesions, and promote initiation and progression of CRC.[91]

12.2. Intestinal dysbiosis in progression of lung cancer: The levels of beneficial bacteria *Actinobacteria species and Bifidobacterium species* were lowered, while the level of harmful bacteria *Enterococcus species* was enhanced in patients with lung cancer.[94] Intestinal dysbiosis is associated with the progression of lung cancer.[93]

12.3. Intestinal dysbiosis in progression of breast cancer: There are different subtypes of breast cancer It has been reported that a distinct microbial pattern was associated with each subtype of breast cancer. For example, the invasive ductal carcinoma had abundance of harmful bacteria such as *Tepidiphilus, Alkanindiges, Stenotrophomonas*, while invasive lobular carcinoma had abundance of *peptostreptococcus, Micromonospora, Faecalibacterium, and Stenotrophomonas*. The levels of toxic bacteria *Porphyromonas, Lacibacter, Ezakiella, and Fusobacterium* were abundant at more advanced stage of the disease compared to lower stage[94] suggesting the role of intestinal dysbiosis in the progression of breast cancer.. Another study reported that the presence of toxic *Bacteroides fragilis* in the gut or breast tissue may increase the aggressiveness of breast tumor leading to metastasis to distant organ.[95]

12.4. Intestinal dysbiosis in progression of leukemia: The composition of gut microbiota influences initiation and progression of acute leukemia, as well as treatment outcome, side-effects, and prognosis of the disease.[96] Intestinal dysbiosis in leukemia causes damage to the intestinal epithelial barrier which allows migration of harmful bacteria to the blood stream or lymph node that leads to inflammatory immune response which may contribute to the development of cancer.[97,98] Intestinal dysbiosis is also associated with the development acute lymphocytic leukemia.[99] Several studies have suggested that intestinal dysbiosis occurs during the onset and treatment of leukemia, and this may reduce the effectiveness of treatment and may predict poor prognosis.[96]

12.5. Intestinal dysbiosis in progression of prostate cancer: It has been suggested that antibiotic treatment activates the inflammatory signaling pathway which contributes to progression of prostate cancer. This was confirmed by experiments which showed that antibiotic-induced intestinal dysbiosis promoted the growth of prostate cancer in a murine model by activating NF-kB-STAT3-IL-6 pathway. In addition, antibiotic treatment markedly increased the number of *Proteobacteria* which is a marker of intestinal dysbiosis.[100] The number of toxic bacteria such as *Bacteriodes, Streptococcus, Rikenellaceae, Alistepes, and Lachomospira* cause growth of prostate cancer cells, and play a role in the development of castration-resistance prostate cancer.[101-103]

12.6. Intestinal dysbiosis in progression of brain cancer: Intestinal dysbiosis inhibits the brain immune function which can affect all stages of brain cancer development and helps tumor cells to evade immune surveillance.[104] Oral dysbiosis is associated with the malignant brain tumor.[105] Oral dysbiosis can also influence the activity of intestinal dysbiosis.[106] and together they can further help in the development and progression of brain tumor. The intestinal dysbiosis contains abundance of *Enterobacteria ceae* in meningioma which suppresses short-chain fatty acid (SCFA) producing bacteria and causes immune dysfunction and unhealthy intestinal environment.[107] The genus *Escherichia/Shigella* were present in large amounts in the brain tumor that can promote chronic inflammation in the brain. The genus *Fusobacterium* and *Akkermansia* are present in in the intestinal dysbiosis that participates in the development and progression of glioma.[104,108]

12.7. Intestinal dysbiosis in progression of melanoma: Skin dysbiosis and intestinal

dysbiosis may play a role in the development and progression of skin melanoma in animal model.[109]

13. Radiation therapy enhances the levels of existing intestinal dysbiosis

It has been reported that radiation therapy enhances the levels of existing intestinal dysbiosis as evidenced by increased number of harmful bacteria such as *proteobacteria and Fusobacteria* and decreased number of beneficial bacteria such as *Biofedobacterium and Faecalibacterium*.[110,111] In addition, chemotherapy and radiation therapy also enhance the levels of intestinal dysbiosis in cancer patients.[112,113]

14. Chemotherapy Enhances the Levels of Existing intestinal dysbiosis.

Chemotherapeutic drugs can directly increase the levels of existing intestinal dysbiosis which damages intestinal epithelial cells, reduce absorption and metabolism of drugs, increase the toxicity of drugs, and reduce their efficacy.[96]

15. Impact of intestinal dysbiosis During and After Chemotherapy and Radiation therapy

Since intestinal dysbiosis is already present in patients with cancer, chemotherapy and radiation therapy further aggravate the levels intestinal dysbiosis which is associated with acute gastrointestinal discomforts that include diarrhea, mucositis, and late adverse effects such as psychoneurological changes, cancer cachexia, and fatigue.[114] Intestinal dysbiosis may enhance development and progression of acute and late adverse effects which impact quality of life during and after treatment as well as survival of patients.[115-118] Therefore, reversing the intestinal dysbiosis by supplementation with probiotics with prebiotics would decrease the risk of development and rate of progression of cancer, and improve the effectiveness of chemotherapy and radiation therapy, and reduce their acute and late adverse effects during treatment.

16. Reversing Intestinal Dysbiosis with Probiotics/Prebiotics That Reduces Acute Side-Effects during Treatment

The main function of probiotics is to restore the balance of bacterial population in favor of beneficial bacteria in the intestine. Prebiotics are soluble and insoluble fibers which provide substrate for fermentation by the beneficial bacteria to produce short-chain fatty acids such as butyric acid which exhibits diverse biological function including anti-cancer.[88,119]

Supplementation with probiotics with prebiotics may be useful in reducing the side effects of chemotherapy and radiation therapy which include decreased risk of infections and improved in recovery of gut damage induced by drugs and its proper function.[120] In addition, probiotics can bind with mutagens and degrades them, lowers intestinal pH, and secrets anti-inflammatory molecules.[24] In a clinical study, supplementation with probiotics containing strains of *lactobacillus* and *Bifedobacterium* alone before chemotherapy and radiation therapy prevented gastrointestinal mucositis. Administration of prebiotics alone before radiation therapy had no impact on the diarrhea in patients with pelvic cancer.[121] A randomized controlled trial involving 60 children with acute leukemia revealed that patients who took probiotics during chemotherapy had significant reduction in most gastrointestinal side-effects including vomiting, nausea, abdominal distension, constipation, and abdominal pain.[122]

Therefore, it is essential that probiotics with prebiotics should be utilized for reducing acute adverse side-effects of cancer treatment. In addition, 60-70% of certain beneficial bacteria such as strains of *Lactobacillus* and *Bifedo* when administered orally is destroyed in the acid pH of the stomach, and more are inactivated in the bile acid of the intestine. This necessitates to add acid resistance probiotics such as *Bacillus coagulans*. The use of such probiotics with prebiotics may reverse intestinal dysbiosis, and thereby, reduce some of the acute and late adverse effects of chemotherapy and radiation therapy.

17. Propose new approaches for improving the effectiveness of Chemotherapy and Radiation therapy and Reducing their toxicity

We propose two approaches to improved effectiveness of chemotherapy and radiation therapy. First approach involves use of a micronutrient mixture containing high doses of multiple antioxidants which would selectively killing of cancer cells by blocking the uptake and metabolism of glucose and glutamine, while producing no such effect on normal cells. This micronutrient mixture would also enhance the growth-inhibitory effects of chemotherapy and radiation therapy on cancer cells by inhibition their uptake and metabolism of glucose and glutamine, while protecting normal cells from their adverse effects. Second approach involves use of probiotics with prebiotics which would reverse the effects of intestinal dysbiosis which play an important role in the progression of cancer, inhibiting the effectiveness of chemotherapy and radiation therapy, and enhancing acute toxicity of these therapies. Clinical studies should be performed using these two approaches at the same time.

18. CONCLUSIONS

Chemotherapy and radiation therapy have produced increased 5-year survival rate in majority of cancers, but they caused acute toxicity during treatment and enhance the risk of neoplastic and non-neoplastic diseases. Although FLASH radiation therapy protects normal cells, but the tumor response rate is like conventional radiation therapy. The late adverse effects of FLASH radiation therapy remain unknown. To increase tumor response rate of chemotherapy and radiation therapy and reduce their acute and late adverse effects, a novel plan is proposed. This plan suggests two independent

approaches which must be simultaneously implemented. First approach recommends the supplementation with a micronutrient mixture containing high doses of multiple antioxidants which would inhibit the growth of cancer cells by blocking the uptake and metabolism of glucose and glutamine which re required for their survival and growth without affecting the growth of normal cells. This micronutrient mixture also enhances the growth-inhibitory effects of chemotherapy and radiation therapy on cancer cells but not on normal cells by the same mechanisms. Tumor cells resistant to chemotherapy and radiation therapy have levels of glutathione. Excessive amounts of free radicals are required for the rapid growth and metastasis of cancer cells; therefore, they have acquired high levels of glutathione to protect themselves from oxidative damage. The propsed micronutrient mixture conaining High doses of multiple antioxidants bypass the protective mechanisms of glutathione by preventing the uptake and metabolism of glucose and glutamine. The validity of the proposed hypothesis for improving treatment of cancer should be tested in pre-clinical and clinical studies.

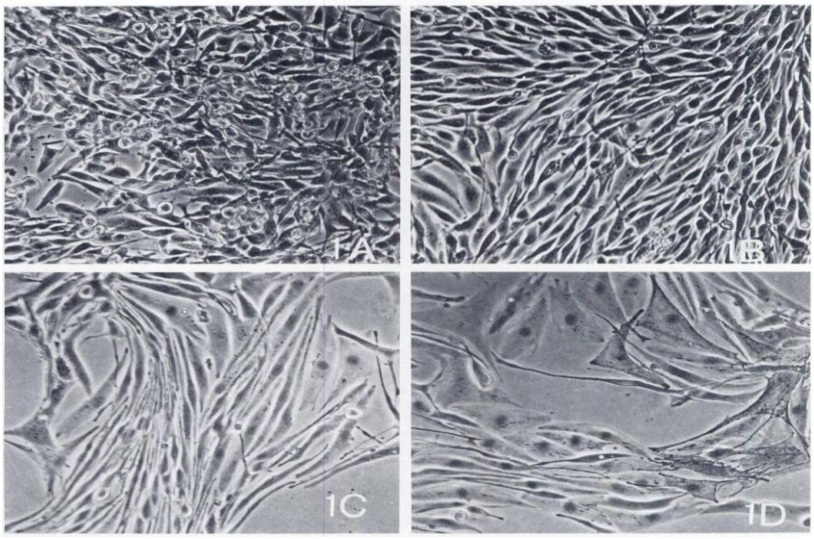

Figure 1: Melanoma cells showing differentiation after treatment with vitamin E succinate. Control melanoma cells without any treatments (1A); Melanoma cell cultures treated with solvent (ethanol 1% and sodium succinate 5-6 µg/ml also exhibited fibroblastic morphology with fewer round cells (1B); alpha-tocopheryl succinate -treated cultures at 6 µg/ml (1C), and 8 µg/ml (1D) showed differentiation and growth inhibition, Mag. X 300.[13]

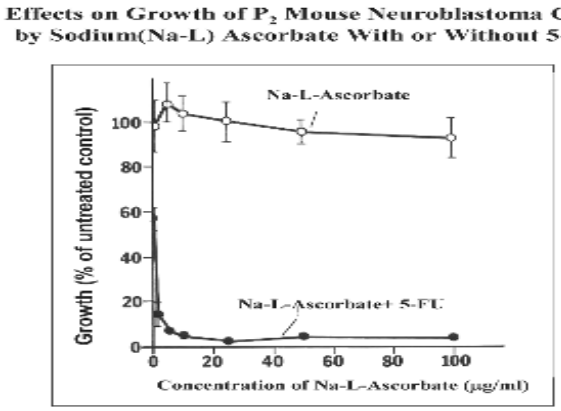

Figure 2: Neuroblastoma cells were plated in tissue culture dishes (60 mm), and 5-fluorouracil (5-FU, 0.08 µg/ml together with various concentration of sodium ascorbate were added 24 hours after plating. Fresh medium, 5-FU, and sodium ascorbate changed 2 days after treatment and cells were counted 3 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.[11]

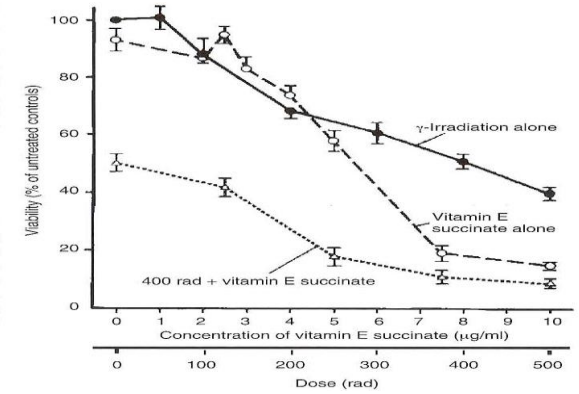

Figure 3: Neuroblastoma cells (NBP2) were gamma-irradiated 24 after plating in tissue culture dishes. Vitamin E succinate or solvent was added immediately before irradiation. Fresh growth medium, vitamin E succinct, and solvent were changed 2 days after irradiation. Cells were counted 3 days later. The 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.[36]

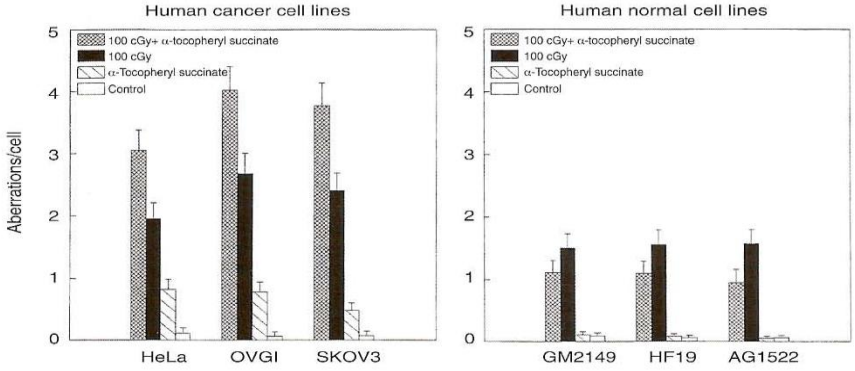

Figure 4: Effect of alpha-tocopheryl succinate on the level of gamma- radiation-induced chromosomal damage in human cervical cancer (HeLa cells), ovarian carcinoma cell line (OVG1 and SKOV3) and human normal fibroblasts (GM2149), HF19, and AG1522). Alpha-tocopheryl succinate treatment increased chromosomal damage as well enhanced radiation-induced chromosomal damage in all 3 cancer cell lines but not in normal cell line.[37,38]

Table 1: 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 ± SE

REFERENCES

1. Favaudon V, Caplier L, Monceau V, Pouzoulet F, Sayarath M, Fouillade C, et al. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. Sci Transl Med, 2014; 6(245): 245ra93.
2. Montay-Gruel P, Petersson K, Jaccard M, Boivin G, Germond JF, Petit B, et al. Irradiation in a flash: Unique sparing of memory in mice after whole brain

irradiation with dose rates above 100Gy/s. Radiother Oncol, 2017; 124(3): 365-9.
3. Montay-Gruel P, Bouchet A, Jaccard M, Patin D, Serduc R, Aim W, et al. X-rays can trigger the FLASH effect: Ultra-high dose-rate synchrotron light source prevents normal brain injury after whole brain irradiation in mice. Radiother Oncol, 2018; 129(3): 582-8.
4. Montay-Gruel P, Acharya MM, Petersson K, Alikhani L, Yakkala C, Allen BD, et al. Long-term neurocognitive benefits of FLASH radiotherapy driven by reduced reactive oxygen species. Proc Natl Acad Sci U S A, 2019; 116(22): 10943-51.
5. Simmons DA, Lartey FM, Schuler E, Rafat M, King G, Kim A, et al. Reduced cognitive deficits after FLASH irradiation of whole mouse brain are associated with less hippocampal dendritic spine loss and neuroinflammation. Radiother Oncol, 2019; 139: 4-10.
6. Vozenin MC, De Fornel P, Petersson K, Favaudon V, Jaccard M, Germond JF, et al. The Advantage of FLASH Radiotherapy Confirmed in Mini-pig and Cat-cancer Patients. Clin Cancer Res, 2019; 25(1): 35-42.
7. Chabi S, To THV, Leavitt R, Poglio S, Jorge PG, Jaccard M, et al. Ultra-high-dose-rate FLASH and Conventional-Dose-Rate Irradiation Differentially Affect Human Acute Lymphoblastic Leukemia and Normal Hematopoiesis. Int J Radiat Oncol Biol Phys, 2021; 109(3): 819-29.
8. Bourhis J, Sozzi WJ, Jorge PG, Gaide O, Bailat C, Duclos F, et al. Treatment of a first patient with FLASH-radiotherapy. Radiother Oncol, 2019; 139: 18-22.
9. Cameron E, Pauling L. Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer. Proc Natl Acad Sci U S A, 1976; 73(10): 3685-9.
10. Cameron E, Pauling L, Leibovitz B. Ascorbic acid and cancer: a review. Cancer Res, 1979; 39(3): 663-81.
11. Prasad KN, Sinha PK, Ramanujam M, Sakamoto A. Sodium ascorbate potentiates the growth inhibitory effect of certain agents on neuroblastoma cells in culture. Proc Natl Acad Sci U S A, 1979; 76(2): 829-32.
12. Prasad KN, Kumar R. Effect of individual and multiple antioxidant vitamins on growth and morphology of human nontumorigenic and tumorigenic parotid acinar cells in culture. Nutrition and cancer, 1996; 26(1): 11-9.
13. Prasad KN, Edwards-Prasad J. Effects of tocopherol (vitamin E) acid succinate on morphological alterations and growth inhibition in melanoma cells in culture. Cancer Res, 1982; 42(2): 550-5.
14. Prasad KN, Cohrs RJ, Sharma OK. Decreased expressions of c-myc and H-ras oncogenes in vitamin E succinate induced morphologically differentiated murine B-16 melanoma cells in culture. Biochem Cell Biol, 1990; 68(11): 1250-5.
15. Kline K, Yu W, Sanders BG. Vitamin E: mechanisms of action as tumor cell growth inhibitors. J Nutr, 2001; 131(1): 161S-3S.
16. Neuzil J, Schroder A, von Hundelshausen P, Zernecke A, Weber T, Gellert N, Weber C. Inhibition of inflammatory endothelial responses by a pathway involving caspase activation and p65 cleavage. Biochemistry, 2001; 40(15): 4686-92.
17. Barnett KT, Fokum FD, Malafa MP. Vitamin E succinate inhibits colon cancer liver metastases. J Surg Res, 2002; 106(2): 292-8.
18. Malafa MP, Fokum FD, Mowlavi A, Abusief M, King M. Vitamin E inhibits melanoma growth in mice. Surgery, 2002; 131(1): 85-91.
19. Malafa MP, Fokum FD, Smith L, Louis A. Inhibition of angiogenesis and promotion of melanoma dormancy by vitamin e succinate. Ann Surg Oncol, 2002; 9(10): 1023-32.
20. Prasad KN. Discovery of Alpha-Tocopheryl Succinate as a Cancer Treatment Agent Led to the Development of Methods to Potentially Improve the Efficacy of Cancer Therapy. J Am Nutr Assoc, 2023; 42(8): 776-82.
21. Hazuka MB, Edwards-Prasad J, Newman F, Kinzie JJ, Prasad KN. Beta-carotene induces morphological differentiation and decreases adenylate cyclase activity in melanoma cells in culture. J Am Coll Nutr, 1990; 9(2): 143-9.
22. Raja SB, Rajendiran V, Kasinathan NK, P A, Venkatabalasubramanian S, Murali MR, et al. Differential cytotoxic activity of Quercetin on colonic cancer cells depends on ROS generation through COX-2 expression. Food Chem Toxicol, 2017; 106(Pt A): 92-106.
23. Chen HY, Lin PH, Shih YH, Wang KL, Hong YH, Shieh TM, et al. Natural Antioxidant Resveratrol Suppresses Uterine Fibroid Cell Growth and Extracellular Matrix Formation In Vitro and In Vivo. Antioxidants (Basel), 2019; 8(4).
24. Folkers K, Brown R, Judy WV, Morita M. Survival of cancer patients on therapy with coenzyme Q10. Biochem Biophys Res Commun, 1993; 192(1): 241-5.
25. Lockwood K, Moesgaard S, Folkers K. Partial and complete regression of breast cancer in patients in relation to dosage of coenzyme Q10. Biochem Biophys Res Commun, 1994; 199(3): 1504-8.
26. Lockwood K, Moesgaard S, Yamamoto T, Folkers K. Progress on therapy of breast cancer with vitamin Q10 and the regression of metastases. Biochem Biophys Res Commun, 1995; 212(1): 172-7.
27. Lesser GJ, Case D, Stark N, Williford S, Giguere J, Garino LA, et al. A randomized, double-blind, placebo-controlled study of oral coenzyme Q10 to relieve self-reported treatment-related fatigue in newly diagnosed patients with breast cancer. J Support Oncol, 2013; 11(1): 31-42.
28. Mortezaee K, Salehi E, Mirtavoos-Mahyari H, Motevaseli E, Najafi M, Farhood B, et al. Mechanisms of apoptosis modulation by curcumin:

Implications for cancer therapy. J Cell Physiol, 2019; 234(8): 12537-50.
29. Aggarwal S, Ichikawa H, Takada Y, Sandur SK, Shishodia S, Aggarwal BB. Curcumin (diferuloylmethane) down-regulates expression of cell proliferation and antiapoptotic and metastatic gene products through suppression of IkappaBalpha kinase and Akt activation. Mol Pharmacol, 2006; 69(1): 195-206.
30. Zhou S, Yao D, Guo L, Teng L. Curcumin suppresses gastric cancer by inhibiting gastrin-mediated acid secretion. FEBS Open Bio, 2017; 7(8): 1078-84.
31. Ojo OA, Adeyemo TR, Rotimi D, Batiha GE, Mostafa-Hedeab G, Iyobhebhe ME, et al. Anticancer Properties of Curcumin Against Colorectal Cancer: A Review. Front Oncol, 2022; 12: 881641.
32. Niedzwiecki A, Roomi MW, Kalinovsky T, Rath M. Anticancer Efficacy of Polyphenols and Their Combinations. Nutrients, 2016; 8(9).
33. Pathak AK, Signh N, Guleria R, Bal S, Thulkar S, Mohanti BK, et al., editors. Role of Vitamins Along with Chemotherapy in Non Small Cell Lung Cancer. International Conference on Nutrition and Cancer, 2002; 3-5 Montevideo-Uruguay.
34. Carr AC, Cook J. Intravenous Vitamin C for Cancer Therapy - Identifying the Current Gaps in Our Knowledge. Front Physiol, 2018; 9: 1182.
35. Bottger F, Valles-Marti A, Cahn L, Jimenez CR. High-dose intravenous vitamin C, a promising multi-targeting agent in the treatment of cancer. J Exp Clin Cancer Res, 2021; 40(1): 343.
36. Sarria A, Prasad KN. dl-alpha-Tocopheryl succinate enhances the effect of gamma-irradiation on neuroblastoma cells in culture. Proc Soc Exp Biol Med, 1984; 175(1): 88-92.
37. Kumar B, Jha MN, Cole WC, Bedford JS, Prasad KN. D-alpha tocopheryl succinate (vitamin E) enhances radiation-induced chromosomal damage levels in human cancer cells, but reduced it in normal cells. J Am Coll Nutr, 2002; 21(4): 339-43.
38. Jha MN, Bedford JS, Cole WC, Edward-Prasad J, Prasad KN. Vitamin E (d-alpha-tocopheryl succinate) decreases mitotic accumulation in gamma-irradiated human tumor, but not in normal, cells. Nutrition and cancer, 1999; 35(2): 189-94.
39. Ripoll EA, Rama BN, Webber MM. Vitamin E enhances the chemotherapeutic effects of adriamycin on human prostatic carcinoma cells in vitro. J Urol, 1986; 136(2): 529-31.
40. Prasad KN, Hernandez C, Edwards-Prasad J, Nelson J, Borus T, Robinson WA. Modification of the effect of tamoxifen, cis-platin, DTIC, and interferon-alpha 2b on human melanoma cells in culture by a mixture of vitamins. Nutrition and cancer, 1994; 22(3): 233-45.
41. Seifter E, Rettura A, Padawar J, Levenson SM. Vitamin A and ß-carotene as Adjunctive Therapy to Tumor Excision, Radiation Therapy and Chemotherapy. In: Prasad KN, editor. Vitamins, Nutrition and Cancer. Basel: Karger, 1984; 1-19.
42. Mills EE. The modifying effect of beta-carotene on radiation and chemotherapy induced oral mucositis. Br J Cancer, 1988; 57(4): 416-7.
43. da Costa Araldi IC, Bordin FPR, Cadona FC, Barbisan F, Azzolin VF, Teixeira CF, et al. The in vitro radiosensitizer potential of resveratrol on MCF-7 breast cancer cells. Chem Biol Interact, 2018; 282: 85-92.
44. Sui X, Zhang C, Zhou J, Cao S, Xu C, Tang F, et al. Resveratrol inhibits Extranodal NK/T cell lymphoma through activation of DNA damage response pathway. J Exp Clin Cancer Res, 2017; 36(1): 133.
45. Rashid A, Liu C, Sanli T, Tsiani E, Singh G, Bristow RG, et al. Resveratrol enhances prostate cancer cell response to ionizing radiation. Modulation of the AMPK, Akt and mTOR pathways. Radiat Oncol, 2011; 6: 144.
46. Hidayat YM, Wagey F, Suardi D, Susanto H, Laihad BJ, Tobing MDL. Analysis of Curcumin as a Radiosensitizer in Cancer Therapy with Serum Survivin Examination: Randomised Control Trial. Asian Pac J Cancer Prev, 2021; 22(1): 139-43.
47. Baek SH, Hong GR, Min DK, Kim EH, Park SK. Effects of Functional Fitness Enhancement through Taekwondo Training on Physical Characteristics and Risk Factors of Dementia in Elderly Women with Depression. Int J Environ Res Public Health, 2021; 18(15).
48. Sanchez Y, Simon GP, Calvino E, de Blas E, Aller P. Curcumin stimulates reactive oxygen species production and potentiates apoptosis induction by the antitumor drugs arsenic trioxide and lonidamine in human myeloid leukemia cell lines. J Pharmacol Exp Ther, 2010; 335(1): 114-23.
49. Mansouri K, Rasoulpoor S, Daneshkhah A, Abolfathi S, Salari N, Mohammadi M, et al. Clinical effects of curcumin in enhancing cancer therapy: A systematic review. BMC Cancer, 2020; 20(1): 791.
50. Prasad KN. Multiple dietary antioxidants enhance the efficacy of standard and experimental cancer therapies and decrease their toxicity. Integr Cancer Ther, 2004; 3(4): 310-22.
51. Rajagopalan KN, DeBerardinis RJ. Role of glutamine in cancer: therapeutic and imaging implications. Journal of nuclear medicine : official publication, Society of Nuclear Medicine, 2011; 52(7): 1005-8.
52. DeBerardinis RJ, Mancuso A, Daikhin E, Nissim I, Yudkoff M, Wehrli S, Thompson CB. Beyond aerobic glycolysis: transformed cells can engage in glutamine metabolism that exceeds the requirement for protein and nucleotide synthesis. Proc Natl Acad Sci U S A, 2007; 104(49): 19345-50.
53. Altman BJ, Stine ZE, Dang CV. From Krebs to clinic: glutamine metabolism to cancer therapy. Nat Rev Cancer, 2016; 16(11): 749.

54. Pliszka M, Szablewski L. Glucose Transporters as a Target for Anticancer Therapy. Cancers (Basel), 2021; 13(16).
55. Eagle H. Nutrition needs of mammalian cells in tissue culture. Science, 1955; 122(3168): 501-14.
56. Yang L, Venneti S, Nagrath D. Glutaminolysis: A Hallmark of Cancer Metabolism. Annu Rev Biomed Eng, 2017; 19: 163-94.
57. Gong T, Zheng C, Ou X, Zheng J, Yu J, Chen S, et al. Glutamine metabolism in cancers: Targeting the oxidative homeostasis. Front Oncol, 2022; 12: 994672.
58. Kodama M, Oshikawa K, Shimizu H, Yoshioka S, Takahashi M, Izumi Y, et al. A shift in glutamine nitrogen metabolism contributes to the malignant progression of cancer. Nat Commun, 2020; 11(1): 1320.
59. Kennedy L, Sandhu JK, Harper ME, Cuperlovic-Culf M. Role of Glutathione in Cancer: From Mechanisms to Therapies. Biomolecules, 2020; 10(10).
60. Fu S, Li Z, Xiao L, Hu W, Zhang L, Xie B, et al. Glutamine Synthetase Promotes Radiation Resistance via Facilitating Nucleotide Metabolism and Subsequent DNA Damage Repair. Cell Rep, 2019; 28(5): 1136-43 e4.
61. Halama A, Suhre K. Advancing Cancer Treatment by Targeting Glutamine Metabolism-A Roadmap. Cancers (Basel), 2022; 14(3).
62. Thiruvalluvan M, Billet S, Bhowmick NA. Antagonizing Glutamine Bioavailability Promotes Radiation Sensitivity in Prostate Cancer. Cancers (Basel), 2022; 14(10).
63. Bhakkiyalakshmi E, Sireesh D, Rajaguru P, Paulmurugan R, Ramkumar KM. The emerging role of redox-sensitive Nrf2-Keap1 pathway in diabetes. Pharmacol Res, 2015; 91: 104-14.
64. Yun J, Mullarky E, Lu C, Bosch KN, Kavalier A, Rivera K, et al. Vitamin C selectively kills KRAS and BRAF mutant colorectal cancer cells by targeting GAPDH. Science, 2015; 350(6266): 1391-6.
65. Vuyyuri SB, Rinkinen J, Worden E, Shim H, Lee S, Davis KR. Ascorbic acid and a cytostatic inhibitor of glycolysis synergistically induce apoptosis in non-small cell lung cancer cells. PLoS One, 2013; 8(6): e67081.
66. El Halabi I, Bejjany R, Nasr R, Mukherji D, Temraz S, Nassar FJ, et al. Ascorbic Acid in Colon Cancer: From the Basic to the Clinical Applications. Int J Mol Sci, 2018; 19(9).
67. Feuerecker B, Pirsig S, Seidl C, Aichler M, Feuchtinger A, Bruchelt G, Senekowitsch-Schmidtke R. Lipoic acid inhibits cell proliferation of tumor cells in vitro and in vivo. Cancer Biol Ther, 2012; 13(14): 1425-35.
68. Jia L, Huang S, Yin X, Zan Y, Guo Y, Han L. Quercetin suppresses the mobility of breast cancer by suppressing glycolysis through Akt-mTOR pathway mediated autophagy induction. Life Sci, 2018; 208: 123-30.
69. Lim HA, Kim JH, Kim JH, Sung MK, Kim MK, Park JH, Kim JS. Genistein induces glucose-regulated protein 78 in mammary tumor cells. J Med Food, 2006; 9(1): 28-32.
70. Keating E, Martel F. Antimetabolic Effects of Polyphenols in Breast Cancer Cells: Focus on Glucose Uptake and Metabolism. Front Nutr, 2018; 5: 25.
71. Moreira L, Araujo I, Costa T, Correia-Branco A, Faria A, Martel F, Keating E. Quercetin and epigallocatechin gallate inhibit glucose uptake and metabolism by breast cancer cells by an estrogen receptor-independent mechanism. Exp Cell Res, 2013; 319(12): 1784-95.
72. Jung KH, Lee JH, Park JW, Quach CHT, Moon SH, Cho YS, Lee KH. Resveratrol-loaded polymeric nanoparticles suppress glucose metabolism and tumor growth in vitro and in vivo. Int J Pharm, 2015; 478(1): 251-7.
73. Gwak H, Haegeman G, Tsang BK, Song YS. Cancer-specific interruption of glucose metabolism by resveratrol is mediated through inhibition of Akt/GLUT1 axis in ovarian cancer cells. Mol Carcinog, 2015; 54(12): 1529-40.
74. Kueck A, Opipari AW, Jr., Griffith KA, Tan L, Choi M, Huang J, et al. Resveratrol inhibits glucose metabolism in human ovarian cancer cells. Gynecol Oncol, 2007; 107(3): 450-7.
75. Jung KH, Lee JH, Thien Quach CH, Paik JY, Oh H, Park JW, et al. Resveratrol suppresses cancer cell glucose uptake by targeting reactive oxygen species-mediated hypoxia-inducible factor-1alpha activation. J Nucl Med, 2013; 54(12): 2161-7.
76. Siddiqui FA, Prakasam G, Chattopadhyay S, Rehman AU, Padder RA, Ansari MA, et al. Curcumin decreases Warburg effect in cancer cells by down-regulating pyruvate kinase M2 via mTOR-HIF1alpha inhibition. Sci Rep, 2018; 8(1): 8323.
77. Soni VK, Mehta A, Ratre YK, Chandra V, Shukla D, Kumar A, Vishvakarma NK. Counteracting Action of Curcumin on High Glucose-Induced Chemoresistance in Hepatic Carcinoma Cells. Front Oncol, 2021; 11: 738961.
78. Liu Z, Peng Q, Li Y, Gao Y. Resveratrol enhances cisplatin-induced apoptosis in human hepatoma cells via glutamine metabolism inhibition. BMB Rep, 2018; 51(9): 474-9.
79. Zhu S, Feng N, Lin G, Tong Y, Jiang X, Yang Q, et al. Metabolic Shift Induced by omega -3 PUFAs and Rapamycin Lead to Cancer Cell Death. Cell Physiol Biochem, 2018; 48(6): 2318-36.
80. Fan WH, Wang FC, Jin Z, Zhu L, Zhang JX. Curcumin Synergizes with Cisplatin to Inhibit Colon Cancer through Targeting the MicroRNA-137-Glutaminase Axis. Curr Med Sci, 2022; 42(1): 108-17.
81. Zhou X, Zheng W, Nagana Gowda GA, Raftery D, Donkin SS, Bequette B, Teegarden D. 1,25-

Dihydroxyvitamin D inhibits glutamine metabolism in Harvey-ras transformed MCF10A human breast epithelial cell. J Steroid Biochem Mol Biol, 2016; 163: 147-56.
82. Perillo B, Di Donato M, Pezone A, Di Zazzo E, Giovannelli P, Galasso G, et al. ROS in cancer therapy: the bright side of the moon. Exp Mol Med, 2020; 52(2): 192-203.
83. Shah MA, Rogoff HA. Implications of reactive oxygen species on cancer formation and its treatment. Semin Oncol, 2021; 48(3): 238-45.
84. Rojo de la Vega M, Chapman E, Zhang DD. NRF2 and the Hallmarks of Cancer. Cancer Cell, 2018; 34(1): 21-43.
85. Ren Z, He Y, Yang Q, Guo J, Huang H, Li B, et al. A Comprehensive Analysis of the Glutathione Peroxidase 8 (GPX8) in Human Cancer. Front Oncol, 2022; 12: 812811.
86. Vogtmann E, Goedert JJ. Epidemiologic studies of the human microbiome and cancer. Br J Cancer, 2016; 114(3): 237-42.
87. Peng L, Li ZR, Green RS, Holzman IR, Lin J. Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase in Caco-2 cell monolayers. J Nutr, 2009; 139(9): 1619-25.
88. Prasad KN. Effect of sodium butyrate in combination with X-irradiation, chemotherapeutic and cyclic AMP stimulating agents on neuroblastoma cells in culture. Experientia, 1979; 35(7): 906-8.
89. Kumar A, Gautam, V., Sandhu, A., Rawat, K., Sharma,A., Saha, L. Current and emerging therapeutic approaches for colorectal cancer: A comprehensive review. World J Gastrointes Surg, 2023; 15(4): 495-519.
90. Kostic AD, Chun E, Robertson L, Glickman JN, Gallini CA, Michaud M, et al. Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. Cell Host Microbe, 2013; 14(2): 207-15.
91. Sun F, Zhang Q, Zhao J, Zhang H, Zhai Q, Chen W. A potential species of next-generation probiotics? The dark and light sides of Bacteroides fragilis in health. Food Res Int, 2019; 126: 108590.
92. Zhuang H, Cheng L, Wang Y, Zhang YK, Zhao MF, Liang GD, et al. Dysbiosis of the Gut Microbiome in Lung Cancer. Front Cell Infect Microbiol, 2019; 9: 112.
93. Xu N, Wang L, Li C, Ding C, Li C, Fan W, et al. Microbiota dysbiosis in lung cancer: evidence of association and potential mechanisms. Transl Lung Cancer Res, 2020; 9(4): 1554-68.
94. Tzeng A, Sangwan N, Jia M, Liu CC, Keslar KS, Downs-Kelly E, et al. Human breast microbiome correlates with prognostic features and immunological signatures in breast cancer. Genome Med, 2021; 13(1): 60.
95. Parida S, Wu S, Siddharth S, Wang G, Muniraj N, Nagalingam A, et al. A Procarcinogenic Colon Microbe Promotes Breast Tumorigenesis and Metastatic Progression and Concomitantly Activates Notch and beta-Catenin Axes. Cancer Discov, 2021; 11(5): 1138-57.
96. Zhou Y, Zhou C, Zhang A. Gut microbiota in acute leukemia: Current evidence and future directions. Front Microbiol, 2022; 13: 1045497.
97. Ivanov, II, Frutos Rde L, Manel N, Yoshinaga K, Rifkin DB, Sartor RB, et al. Specific microbiota direct the differentiation of IL-17-producing T-helper cells in the mucosa of the small intestine. Cell Host Microbe, 2008; 4(4): 337-49.
98. Tsilimigras MC, Fodor A, Jobin C. Carcinogenesis and therapeutics: the microbiota perspective. Nat Microbiol, 2017; 2: 17008.
99. Strick R, Strissel PL, Borgers S, Smith SL, Rowley JD. Dietary bioflavonoids induce cleavage in the MLL gene and may contribute to infant leukemia. Proc Natl Acad Sci U S A, 2000; 97(9): 4790-5.
100. Zhong W, Wu K, Long Z, Zhou X, Zhong C, Wang S, et al. Gut dysbiosis promotes prostate cancer progression and docetaxel resistance via activating NF-kappaB-IL6-STAT3 axis. Microbiome, 2022; 10(1): 94.
101. Fujita K, Matsushita M, De Velasco MA, Hatano K, Minami T, Nonomura N, Uemura H. The Gut-Prostate Axis: A New Perspective of Prostate Cancer Biology through the Gut Microbiome. Cancers (Basel), 2023; 15(5).
102. Golombos DM, Ayangbesan A, O'Malley P, Lewicki P, Barlow L, Barbieri CE, et al. The Role of Gut Microbiome in the Pathogenesis of Prostate Cancer: A Prospective, Pilot Study. Urology, 2018; 111: 122-8.
103. Matsushita M, Fujita K, Motooka D, Hatano K, Fukae S, Kawamura N, et al. The gut microbiota associated with high-Gleason prostate cancer. Cancer Sci, 2021; 112(8): 3125-35.
104. Lin B, Ye Z, Ye Z, Wang M, Cao Z, Gao R, Zhang Y. Gut microbiota in brain tumors: An emerging crucial player. CNS Neurosci Ther, 2023; 29, 1(1): 84-97.
105. Wen Y, Feng L, Wang H, Zhou H, Li Q, Zhang W, et al. Association Between Oral Microbiota and Human Brain Glioma Grade: A Case-Control Study. Front Microbiol, 2021; 12: 746568.
106. Hou W, Li J, Cao Z, Lin S, Pan C, Pang Y, Liu J. Decorating Bacteria with a Therapeutic Nanocoating for Synergistically Enhanced Biotherapy. Small, 2021; 17(37): e2101810.
107. Yoo JY, Groer M, Dutra SVO, Sarkar A, McSkimming DI. Gut Microbiota and Immune System Interactions. Microorganisms, 2020; 8(10).
108. Brennan CA, Garrett WS. Fusobacterium nucleatum - symbiont, opportunist and oncobacterium. Nat Rev Microbiol, 2019; 17(3): 156-66.
109. Mekadim C, Skalnikova HK, Cizkova J, Cizkova V, Palanova A, Horak V, Mrazek J. Dysbiosis of skin microbiome and gut microbiome in melanoma progression. BMC Microbiol, 2022; 22(1): 63.

110. Li Z, Ke X, Zuo D, Wang Z, Fang F, Li B. New Insights into the Relationship between Gut Microbiota and Radiotherapy for Cancer. Nutrients, 2022; 15(1).
111. Fernandes A, Oliveira A, Soares R, Barata P. The Effects of Ionizing Radiation on Gut Microbiota, a Systematic Review. Nutrients, 2021; 13(9).
112. El Alam MB, Sims TT, Kouzy R, Biegert GWG, Jaoude J, Karpinets TV, et al. A prospective study of the adaptive changes in the gut microbiome during standard-of-care chemoradiotherapy for gynecologic cancers. PLoS One, 2021; 16(3): e0247905.
113. Oliva M, Schneeberger PHH, Rey V, Cho M, Taylor R, Hansen AR, et al. Transitions in oral and gut microbiome of HPV+ oropharyngeal squamous cell carcinoma following definitive chemoradiotherapy (ROMA LA-OPSCC study). Br J Cancer, 2021; 124(9): 1543-51.
114. Maddern AS, Coller JK, Bowen JM, Gibson RJ. The Association between the Gut Microbiome and Development and Progression of Cancer Treatment Adverse Effects. Cancers (Basel), 2023; 15(17).
115. Al-Qadami G, Bowen J, Van Sebille Y, Secombe K, Dorraki M, Verjans J, et al. Baseline gut microbiota composition is associated with oral mucositis and tumour recurrence in patients with head and neck cancer: a pilot study. Support Care Cancer, 2023; 31(1): 98.
116. Gonzalez-Mercado VJ, Lim J, Marrero S, Pedro E, Saligan LN. Gut microbiota and fatigue in rectal cancer patients: a cross-sectional pilot study. Support Care Cancer, 2021; 29(8): 4615-21.
117. Hakozaki T, Nolin-Lapalme A, Kogawa M, Okuma Y, Nakamura S, Moreau-Amaru D, et al. Cancer Cachexia among Patients with Advanced Non-Small-Cell Lung Cancer on Immunotherapy: An Observational Study with Exploratory Gut Microbiota Analysis. Cancers (Basel), 2022; 14(21).
118. Paulsen JA, Ptacek TS, Carter SJ, Liu N, Kumar R, Hyndman L, et al. Gut microbiota composition associated with alterations in cardiorespiratory fitness and psychosocial outcomes among breast cancer survivors. Support Care Cancer, 2017; 25(5): 1563-70.
119. Prasad KN. Butyric acid: a small fatty acid with diverse biological functions. Life Sci, 1980; 27(15): 1351-8.
120. Martyniak A, Zakrzewska Z, Schab M, Zawartka A, Wedrychowicz A, Skoczen S, Tomasik PJ. Prevention and Health Benefits of Prebiotics, Probiotics and Postbiotics in Acute Lymphoblastic Leukemia. Microorganisms, 2023; 11(7).
121. Sasidharan BK, Ramadass B, Viswanathan PN, Samuel P, Gowri M, Pugazhendhi S, Ramakrishna BS. A phase 2 randomized controlled trial of oral resistant starch supplements in the prevention of acute radiation proctitis in patients treated for cervical cancer. J Cancer Res Ther, 2019; 15(6): 1383-91.
122. Reyna-Figueroa J, Barron-Calvillo E, Garcia-Parra C, Galindo-Delgado P, Contreras-Ochoa C, Lagunas-Martinez A, et al. Probiotic Supplementation Decreases Chemotherapy-induced Gastrointestinal Side Effects in Patients With Acute Leukemia. J Pediatr Hematol Oncol, 2019; 41(6): 468-72.