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HIGH DOSE ANTIOXIDANTS WITH PROBIOTICS SELECTIVELY KILL CANCER CELLS AND ENHANCE EFFECTIVENESS OF CANCER THERAPIES ON CANCER CELLS WITHOUT AFFECTING NORMAL CELLS

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ABSTRACT
Chemo/radiation therapy have increased 5-year survival rate in most cancers; however, acute and late adverse side-effects of treatment remain. Therefore, a new approach to reduce toxicity and improve survival rate is needed. In 2014, FLASH radiation therapy which delivers radiation dose to tumor at a dose rate of 40 Gy/sec compared to dose rate of 0.01 Gy/sec of conventional radiation therapy protected normal tissue against acute injury, while the tumor response rate was like conventional radiation therapy. Therefore, another new approach is needed. Individual antioxidants such as vitamin C and vitamin E succinate at high doses inhibit the growth of cancer cells and enhance the effects of chemotherapeutic agents and x-irradiation on cancer cells, while protecting or no significant effects on normal cells in culture. While searching for mechanisms of high dose antioxidants, it was found that cancer cells require glucose and glutamine for their survival. This led us to propose that high doses of antioxidants kill cancer cells by inhibiting the uptake and metabolism of these nutrients. Some antioxidants prevent uptake of glucose, while others prevent the uptake of glutamine by cancer cells. Therefore, we developed of a formulation of high doses of multiple antioxidants which may kill tumor cells by inhibiting the uptake of glucose and glutamine and enhance the effectiveness of chemo/radiation therapy while reducing their toxicity Since Intestinal dysbiosis participates in the development and progression of cancer and reduces the effectiveness of current therapies, we propose that combining probiotics and prebiotics with high doses of multiple antioxidants before, during, and after treatment may markedly enhance survival rate of patients more than produced by current therapies, while reducing their side-effects.

KEYWORDS: High dose antioxidants; probiotics; cancer therapies; glucose; glutamine.

INTRODUCTION
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. In 2010, 569,000, in 2020, 602,000 and in 2024, approximately 611,720 people died from this disease. 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 and appearance of second primary cancers. In addition, damage to the brain**,** bone, endocrine system, eyes, hearing, heart, lung, joints, and mouth, if these organs are involved in the treatment area with chemotherapy and/or radiation therapy.[1,2] To improve radiation treatment, in 2014, a new technology referred to as FLASH radiation therapy which delivers radiation dose to tumor at a dose rate of 40 Gy/sec compared to dose rate of 0.01 Gy/sec of conventional radiation therapy CONV-RT) was developed. This therapy protected normal tissue against acute radiation injury, but the tumor repones rate was like CONV-RT.[3] Therefore,

another novel approach which can enhance the survival rate of both FLASH-RT and CONV-RT and reduce their toxicity is needed.

This review proposes a novel approach which includes supplementation with high doses of multiple antioxidants in combination with probiotics and prebiotics before, during, and after exposure to FLASH-RT or CONV-RT may further enhance 5-year survival rate of all cancer types and reduce the acute and late adverse effects of these therapies. Application of high doses of would be equally effective against chemotherapy.

Supplementation With High Doses of Antioxidants Inhibit the Growth of Cancer Without Affecting Normal Cells

Doses of individual antioxidant or multiple antioxidants which kill cancer cells but not normal cells in culture or in vivo would be considered high dose. On the other hand, doses of individual antioxidant or multiple antioxidants which do not kill cancer cells and normal cells in culture or in vivo would be considered low dose.

Mechanism of action differs between low and high dose antioxidant: Low doses of antioxidant protect normal and cancer cells from free radical damage, while high doses of multiple antioxidants kill cancer cells by blocking the uptake and metabasin of glucose and glutamine without affecting normal cells.

Experimental Studies with High Doses of Individual Antioxidants on Cancer and Normal Cells in Culture

Effects of high doses of vitamin C: In1976, Dr. Linus Pauling and his colleague were first to demonstrate that high doses of vitamin C alone inhibited the growth of cancer cells in humans.[4,5] This observation created a lot of controversy among oncologists. The above observation could not be confirmed in another clinical study on human.[6] We decided to test Dr. Pauling observation on murine neuroblastoma (NB) cells in culture and found that high doses of vitamin C as sodium ascorbate killed NB cells in culture, however, the growth of murine fibroblasts was minimally affected. In addition, we showed that vitamin C at high doses enhances the growth-inhibitory effects of x-irradiation and chemotherapeutic agents on neuroblastoma cells in culture without significantly affecting normal fibroblasts. Vitamin C at high 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.[7]

High doses of vitamin E succinate: In 1982, we discovered that d-alpha-tocopheryl succinate (vitamin E succinate) at high doses induced differentiation and growth inhibition in murine melanoma cells in culture.[8] Vitamin E succinate at a high dose reduced the expression of oncogenes c-myc and H-ras in melanoma cells in culture.[9] Several studies using other cancer cell lines in culture and in animal models of cancer confirmed this observation.[10-13] A recent review has further documented the role of vitamin E succinate in inhibiting the growth of tumor cells.[14] However, no such studies on human cancer have been performed.

High doses of beta-carotene or retinol: Treatment with high doses of beta-carotene or retinol induced differentiation in murine neuroblastoma cells and B-16 murine melanoma cells in culture, respectively, and inhibited their growth.[15]

High doses of quercetin: Overexpression of cyclooxygenase (COX-2) plays a significant role in the development and progression of cancer. Treatment with high doses of quercetin increased apoptosis and inhibited the growth of human colon cancer cells (HT29 cells) over-expressing Cox-2 enzyme without significant effect on the growth of normal epithelial cell line (IEC-6).[16]

High doses of 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.[17]

High doses of coenzyme Q10: Daily supplementation of coenzyme Q10 at a high dose of 390 mg or more daily may increase the survival time of breast cancer patients receiving standard cancer therapy.[18-20] 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.[21]

High doses of curcumin: Treatment with high doses of curcumin reduced the growth and caused apoptosis in various cancer cells in culture including gastric carcinoma and colon cancer cells.[22-25]

High doses of antioxidant mixture: Treatment with a mixture of antioxidants containing high doses of ascorbic acid, quercetin, green tea extract, lysine, and proline inhibited the growth of human ovarian cells in culture and in athymic mice.[26] The elimination of quercetin from this mixture did not affect the potency of this mixture in inhibiting the growth of human retinoblastoma cells in culture and in athymic mice[27], human leukemic cell line (U-93,) and head and neck squamous cell carcinoma cell line (FaDu) in culture and in athymic mice.[28] Treatment with another antioxidant mixture containing high doses of quercetin, curcumin, resveratrol, green tea extract, and cruciferex also reduced the growth of human head and neck squamous cell carcinoma in culture (OHSU-974 cell line) and in athymic mice as well as in fibrosarcoma (HT-180 cell line) and melanoma (A2058 cell line).[29] 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.[30] Another mixture of antioxidants containing vitamin C, retinoic acid, polar carotenoids, and d-alpha-tocopheryl succinate even at non-growth-inhibitory dose reduced the growth of human melanoma cells in culture by about 50%. 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 in the same mixture dramatically reduced the growth of melanoma cells in culture.[31] This suggests that high doses of all four antioxidants in combination 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.[7] These studies suggest that high doses of antioxidants kill cancer cells but not normal cells.[32-34]

Do Cancer Cells Require Specific Nutrients for Their Survival and Growth?

While searching for the mechanisms of action of high doses of antioxidants on tumor cells, the question arose whether cancer cells require specific nutrients for their survival and growth and whether high doses of antioxidants block uptake and metabolism of these nutrients only in cancer cells. Search of published studies revealed that all cancer cells require glucose and glutamine metabolism for their survival and growth. Glucose is needed to produce energy, while glutamine is essential for making vital molecules such as protein and nucleic acid.

Requirements of glucose: All cancer cells require excessive amounts of glucose, because they 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 exhibit increased expression of glucose transporter-1 (GLUT-1) and glucose transporter-3 (GLUT-3) that enhance the uptake of glucose causing accumulation of glucose in the cells. Excess glucose in cancer cells is oxidized to produce extensive amounts free radicals which are required for the proliferation and metastasis of cancer cells.[35] In addition, increased accumulation of glucose leads to more production of lactic acid making cellular environment acidic which favors growth of cancer cells.[36] Inhibitors of glucose transporters GLUT-1 and GLUT-3 increase the death of cancer cell by inhibiting the uptake of glucose.[37]

Requirement of glutamine: All cancer cells require glutamine uptake and metabolism for their survival and growth[38], because it provides source of energy, and nitrogen for protein and nucleic acid synthesis that are essential for their survival and growth.[39] Therefore, preventing the uptake of glutamine may cause death of cancer cells. It has been demonstrated that reducing the availability of glutamine promotes radiosensitivity of prostate cancer.[40] It has been shown that inhibition of glutamine metabolism increases the sensitivity of Kras positive pancreatic ductal adenocarcinoma to radiation therapy[41] These studies indicate that the inhibition of uptake or metabolism of glutamine can cause death of tumor cells.

Based on the above studies, we suggested that the mechanism of action of high doses of antioxidants may involve inhibition of the uptake and metabolism of glucose and glutamine. This may account for the selective death of cancer cells following administration of a mixture of high doses of antioxidants. A literature search concerning this suggestion was confirmed this idea. Some examples are given:

High Doses of Individual Antioxidants Kill Cancer Cells by Inhibiting Glucose Uptake and Metabolism

Vitamin C: Treatment with high dose of vitamin C inhibited glycolysis creating energy crisis causing death of several types of cancer cells. These include human colorectal cancer (CRC cell line) carrying Kras mutation or Braf mutation that makes them resistance to standard therapies[42], non-small cell lung cancer cells[43], and colon cancer.[44]

Alpha-lipoic acid: Treatment with alpha-lipoic acid at high doses reduced glucose uptake and reduced the growth of neuroblastoma cells and breast cancer cells (SKBr3 cell line) in culture and also on transplanted tumor in a thymic mouse.[45]

Quercetin and Epigallocatechin Gallate (EGCG): Treatment with quercetin blocked the uptake of glucose leading to inhibition of glycolysis causing growth inhibition of tumor cells in culture. This also 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). Quercetin also inhibited tumor growth and metastasis by inhibiting glycolysis in vivo.[46] Both quercetin and EGCG inhibited the uptake of glucose and reduced the growth of estrogen receptor (ER)-positive cell line (MCF7) and ER-negative cell line (MDA-MB-231) breast cancer cells in culture.[47]

Resveratrol: Treatment with 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.[48] Resveratrol induced apoptosis in ovarian cancer cells in culture by inhibiting the uptake of glucose[49] 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).[50]

Curcumin: Treatment with curcumin at high doses inhibited glucose uptake in variety of cancer cells and reduced their growth.[51] It also prevented glucose-induced chemoresistance by blocking the uptake of glucose in hepatic carcinoma cells.[52]

High Doses of Individual Antioxidants Kill Cancer Cells by Inhibiting Glutamine Uptake and Metabolism

Resveratrol: Treatment with resveratrol enhanced cisplatin-induced apoptosis in hepatoma cells in culture by inhibiting glutamine metabolism.[53]

Curcumin: Curcumin treatment in combination with cisplatin suppressed proliferation of colon cancer cells in a synergistic manner. In addition, curcumin treatment overcame cisplatin resistance in colon cancer cells by inhibiting the uptake of glutamine.[54]

Vitamin D3: Treatment with vitamin D3 at a high 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.[55]

Causes of Cancer Cells to Develop Resistant to Therapies and Proposed Suggestion to Overcome Them

A nuclear transcriptional factor, Nrf2 is constitutively expressed in cancer cells.[56] 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, enhance level of glutathione that protects cancer cells from oxidative damage and make them resistant to therapeutic agents.[57] We propose that high doses of multiple antioxidants would bypass the effect of these protective mechanisms and kill treatment resistant cancer cells by blocking the uptake and metabolism of glucose and glutamine. (High dose antioxidant in cancer treatment has received US Patent No 11,938,152, B2).

Supplementation Probiotics with Prebiotics may Improve Effectiveness of Therapies

The role of intestinal dysbiosis (increase in the number of harmful bacteria and decline in the number of beneficial bacteria) in the treatment of cancer has not drawn significant attention from oncologists. Intestinal dysbiosis contributes to the initiation and progression of colorecta cancer[58], lung cancer[59], breast cancer[60], prostate cancer[61], and brain tumors[62] and reduces the effectiveness of chemotherapy and radiation therapy.[63-65] Therefore, we propose that supplementation with probiotics with prebiotics together with high doses multiple antioxidants before, during, and after treatment may reverse the harmful effects of intestinal dysbiosis and increase further survival time and decrease their acute and late adverse side-effects.

Interim Cancer Protocol Using High Doses of Multiple Antioxidants

1. Use of a high doses of multivitamins: Since there are several experimental studies to support the value of high doses of multiple antioxidants in cancer treatment, and since patented antioxidants was not available, I developed an interim cancer treatment protocol which can be used in consultation with oncologist. This protocol involves taking a multivitamins 3 times of normal dose after breakfast, after lunch, and after dinner. Each patient will receive about 17 gm of total amounts of multiple antioxidants before, during, and after chemo or radiation therapy. This total dose of multiple antioxidants is similar to the patented "high dose antioxidants in cancer treatment" US Patent No 11,938,152, B2 which has 16.8 gm of multiple antioxidants. This protocol also includes taking commercially sold probiotics with prebiotics (One capsule in the morning and one in the evening). This interim cancer treatment protocol was not approved by any state, Federal, or any company. Adopting the interim protocol depended upon patients and their oncologists.

Several cancer patients have used this cancer interim cancer treatment protocol, most of them used in combination with chemo and radiation therapy, a few of them used without standard therapy. One example of each is presented here. Seeking fund to initiate phase I,II, and phase III trials on my patented "High dose antioxidants in cancer treatment".

Patient number 1

He was diagnosed with basal cell carcinoma back in 2019. He had Mohs surgery done and the doctor thought that he had gotten all of it. Two years later he noticed that this lump under his eye was getting bigger and two different doctors, Dr Atlas, oncologist at Levine, and Dr Raghavan the oncologist he saw at the VA, told us that it was no longer scar tissue, and they tested him. The VA sent him to Emory Proton Beam in Atlanta in Aug of 2023 for radiation treatment. He started using interim protocol during his treatments. It protected him from hair loss, fatigue and all the other side effects they told him about! He had a recheck at Emory in December. They did an MRI and CT scan and said the tumor was gone. They gave us a copy of the before and after scan! We go back in June for his last recheck.

This photo is most recent.

Patient 2.

Study Summary: Rapid Healing of Stage 3 Melanoma in Ecuador

A woman in Ecuador was diagnosed with **stage 3 melanoma** on the bottom of her foot (A).

She had two open, pus-filled sores that caused severe pain, fatigue, and depression.

Doctors warned that the cancer could rapidly spread through her bloodstream and discussed possible **amputation** to save her life.

Timeline of Events: April 16, 2024: Diagnosis confirmed with concerns about rapid cancer progression. **April 18, 2024**: The patient began taking Interim protocol guided by Charlie Rayford.

April 22, 2024 (Day 5):Visible improvement: sores began drying up (B). Pain, fatigue, and depression were eliminated. Increased energy and mobility reported. **April 27, 2024 (Day 10)**: The sores were nearly closed. The patient experienced significant quality-of-life improvements, including restored personality and mobility. **April 30, 2024 (Day 13)**: Wounds completely healed externally (C).

The patient resumed walking and normal activities without pain.

No chemotherapy or radiation had been initiated by this point.

Emotional Recovery: Depression lifted, improving the emotional state of the entire family.

Physical Recovery: Complete external wound closure within 13 days; restored energy and mobility.

Avoided Amputation: The patient retained her leg and achieved normal functionality.

First figure (A); Second figure (B); and Third figure (C)

CONCLUSIONS

Chemotherapy and radiation therapy have increased 5-year survival rate in majority of cancers; however, acute and late adverse effects of these therapies remain a major concern of oncologists. Therefore, a new approach to improve clinical outcome is needed. In 2014, a new technology referred to as FLASH radiation therapy which delivers radiation dose to tumor at a dose rate of 40 Gy/sec compared to dose rate of 0.01 Gy/sec of conventional radiation therapy was developed. This form of therapy protected normal tissue against acute injury, but the tumor repose rate was like conventional radiation therapy. Therefore, another approach is needed. This review proposes supplementation with high doses of multiple antioxidants and probiotics with prebiotics before, during, and after chemotherapy and/or radiation may markedly improve 5-year survival rate and reduce the adverse effects of therapies. All cancer cells require uptake and metabolism of glucose and glutamine for their survival and growth, and high doses of antioxidants block the uptake and metabolism of these nutrients in cancer cells, and thereby, selectively kill cancer cells but not normal cells. Since intestinal dysbiosis participates in the initiation and progression of cancer and reduce the effectiveness of current therapies, combining probiotics with prebiotics and high doses of antioxidants together before, during, and after chemotherapy and/or radiation therapy may markedly enhance further survival rate and decrease acute and late adverse effects of these therapies.

Since there are several experimental studies to support the value of high doses of multiple antioxidants in cancer treatment, I developed an interim cancer protocol of high doses of multiple antioxidants which can be used in consultation with oncologist. This protocol involves taking a multivitamins 3 times of normal dose after breakfast, after lunch, and after dinner. Each patient will receive about 17 gm of total amounts of multiple antioxidants before, during, and after chemo or radiation therapy. This total dose of multiple antioxidants is like patented " high dose antioxidants in cancer treatment" US Patent No 11,938,152, B2 which has 16.8 gm of multiple antioxidants, and one capsule of Probiotics with prebiotics in the morning and one in the evening.

Ethical Statement: Since it is a review manuscript, ethical statement is not needed. Any ethical statement related to a review paper has been met.

Conflict: The author is Chief Scientific Officer of Engage Global of Utah. This company sells nutritional products to consumers.

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REFERENCES

1. Sung, H.; Hyun, N.; Leach, C. R.; Yabroff, K. R.; Jemal, A. Association of First Primary Cancer With Risk of Subsequent Primary Cancer Among Survivors of Adult-Onset Cancers in the United States. *JAMA*, 2020; *324*(24): 2521-2535. DOI: 10.1001/jama.2020.23130.
2. Jung, A. Y.; Cai, X.; Thoene, K.; Obi, N.; Jaskulski, S.; Behrens, S.; Flesch-Janys, D.; Chang-Claude, J. Antioxidant supplementation and breast cancer prognosis in postmenopausal women undergoing chemotherapy and radiation therapy. *Am J Clin*

Nutr., 2019; *109*(1): 69-78. DOI: 10.1093/ajcn/nqy223 From NLM Medline.
3. Favaudon, V.; Caplier, L.; Monceau, V.; Pouzoulet, F.; Sayarath, M.; Fouillade, C.; Poupon, M. F.; Brito, I.; Hupe, P.; Bourhis, J.; et al. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. *Sci Transl Med.*, 2014; *6*(245): 245ra293. DOI: 10.1126/scitranslmed.3008973.
4. Cameron, E.; Pauling, L. Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer. *Proc Natl Acad Sci USA.*, 1976; *73*(10): 3685-3689. DOI: 10.1073/pnas.73.10.3685.
5. Cameron, E.; Pauling, L.; Leibovitz, B. Ascorbic acid and cancer: a review. *Cancer Res.*, 1979; *39*(3): 663-681.
6. Creagan, E. T.; Moertel, C. G.; O'Fallon, J. R.; Schutt, A. J.; O'Connell, M. J.; Rubin, J.; Frytak, S. Failure of high-dose vitamin C (ascorbic acid) therapy to benefit patients with advanced cancer. A controlled trial. *N Engl J Med.*, 1979; *301*(13): 687-690. DOI: 10.1056/NEJM197909273011303 From NLM Medline.
7. Prasad, K. N.; Kumar, R. Effect of individual and multiple antioxidant vitamins on growth and morphology of human nontumorigenic and tumorigenic parotid acinar cells in culture. *Nutr Cancer*, 1996; *26*(1): 11-19.
8. Prasad, K. N.; 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): 550-555.
9. Prasad, K. N.; Cohrs, R. J.; Sharma, O. K. 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): 1250-1255.
10. Barnett, K. T.; Fokum, F. D.; Malafa, M. P. Vitamin E succinate inhibits colon cancer liver metastases. *J Surg Res.*, 2002; *106*(2): 292-298.
11. Kline, K.; Yu, W.; Sanders, B. G. Vitamin E: mechanisms of action as tumor cell growth inhibitors. *J Nutr.*, 2001; *131*(1): 161S-163S.
12. 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): 4686-4692.
13. Malafa, M. P.; Fokum, F. D.; Mowlavi, A.; Abusief, M.; King, M. Vitamin E inhibits melanoma growth in mice. *Surgery*, 2002; *131*(1): 85-91.
14. Prasad, K. N. 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): 776-782. DOI: 10.1080/27697061.2023.2175389.
15. Hazuka, M. B.; Edwards-Prasad, J.; Newman, F.; Kinzie, J. J.; Prasad, K. N. Beta-carotene induces morphological differentiation and decreases adenylate cyclase activity in melanoma cells in culture. *J Am Coll Nutr.*, 1990; *9*(2): 143-149.
16. Raja, S. B.; Rajendiran, V.; Kasinathan, N. K.; P, A.; Venkatabalasubramanian, S.; Murali, M. R.; Devaraj, H.; Devaraj, S. N. 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. DOI: 10.1016/j.fct.2017.05.006.
17. Chen, H. Y.; Lin, P. H.; Shih, Y. H.; Wang, K. L.; Hong, Y. H.; Shieh, T. M.; Huang, T. C.; Hsia, S. M. Natural Antioxidant Resveratrol Suppresses Uterine Fibroid Cell Growth and Extracellular Matrix Formation In Vitro and In Vivo. *Antioxidants (Basel)*, 2019; *8*(4). DOI: 10.3390/antiox8040099.
18. Folkers, K.; Brown, R.; Judy, W. V.; Morita, M. Survival of cancer patients on therapy with coenzyme Q10. *Biochem Biophys Res Commun*, 1993; *192*(1): 241-245. DOI: 10.1006/bbrc.1993.1405.
19. 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): 1504-1508. DOI: 10.1006/bbrc.1994.1401.
20. 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): 172-177. DOI: 10.1006/bbrc.1995.1952.
21. Lesser, G. J.; Case, D.; Stark, N.; Williford, S.; Giguere, J.; Garino, L. A.; Naughton, M. J.; Vitolins, M. Z.; Lively, M. O.; Shaw, E. G.; 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. DOI: 10.1016/j.suponc.2012.03.003.
22. Mortezaee, K.; Salehi, E.; Mirtavoos-Mahyari, H.; Motevaseli, E.; Najafi, M.; Farhood, B.; Rosengren, R. J.; Sahebkar, A. Mechanisms of apoptosis modulation by curcumin: Implications for cancer therapy. *J Cell Physiol*, 2019; *234*(8): 12537-12550. DOI: 10.1002/jcp.28122.
23. Aggarwal, S.; Ichikawa, H.; Takada, Y.; Sandur, S. K.; Shishodia, S.; Aggarwal, B. B. 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. DOI: 10.1124/mol.105.017400.
24. Zhou, S.; Yao, D.; Guo, L.; Teng, L. Curcumin suppresses gastric cancer by inhibiting gastrin-mediated acid secretion. *FEBS Open Bio.*, 2017; *7*(8): 1078-1084. DOI: 10.1002/2211-5463.12237.
25. Ojo, O. A.; Adeyemo, T. R.; Rotimi, D.; Batiha, G. E.; Mostafa-Hedeab, G.; Iyobhebhe, M. E.; Elebiyo,

T. C.; Atunwa, B.; Ojo, A. B.; Lima, C. M. G.; et al. Anticancer Properties of Curcumin Against Colorectal Cancer: A Review. *Front Oncol*, 2022; *12:* 881641. DOI: 10.3389/fonc.2022.881641.

26. Roomi, M. W.; Kalinovsky, T.; Rath, M.; Niedzwiecki, A. A Specific Mixture of Nutrients Suppresses Ovarian Cancer A-2780 Tumor Incidence, Growth, and Metastasis to Lungs. *Nutrients*, 2017; *9*(3). DOI: 10.3390/nu9030303.
27. Roomi, M. W.; Roomi, N.; Bhanap, B.; Niedzwiecki, A.; Rath, M. Antineoplastic activity of a nutrient mixture in Y-79 malignant retinoblastoma cells. *Oncol Rep.*, 2013; *29*(1): 29-33. DOI: 10.3892/or.2012.2110.
28. Roomi, M. W.; Roomi, N. W.; Kalinovsky, T.; Rath, M.; Niedzwiecki, A. Marked inhibition of growth and invasive parameters of head and neck squamous carcinoma FaDu by a nutrient mixture. *Integr Cancer Ther.*, 2009; *8*(2): 168-176. DOI: 10.1177/1534735408334632.
29. Niedzwiecki, A.; Roomi, M. W.; Kalinovsky, T.; Rath, M. Anticancer Efficacy of Polyphenols and Their Combinations. *Nutrients*, 2016; *8*(9). DOI: 10.3390/nu8090552.
30. Pathak, A. K.; Signh, N.; Guleria, R.; Bal, S.; Thulkar, S.; Mohanti, B. K.; Gupta, S.; Khanna, N.; Reddy, V. G.; Thakur, M. B.; et al. Role of Vitamins Along with Chemotherapy in Non Small Cell Lung Cancer. In *International Conference on Nutrition and Cancer*, Montevideo-Uruguay, October 3-5, 2002; 28.
31. Prasad, K. N.; Hernandez, C.; Edwards-Prasad, J.; Nelson, J.; Borus, T.; Robinson, W. A. 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): 233-245.
32. Rajagopalan, K. N.; DeBerardinis, R. J. Role of glutamine in cancer: therapeutic and imaging implications. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*, 2011; *52*(7): 1005-1008. DOI: 10.2967/jnumed.110.084244.
33. DeBerardinis, R. J.; Mancuso, A.; Daikhin, E.; Nissim, I.; Yudkoff, M.; Wehrli, S.; Thompson, C. B. 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): 19345-19350. DOI: 10.1073/pnas.0709747104.
34. Altman, B. J.; Stine, Z. E.; Dang, C. V. From Krebs to clinic: glutamine metabolism to cancer therapy. *Nat Rev Cancer*, 2016; *16*(11): 749. DOI: 10.1038/nrc.2016.114.
35. Panieri, E.; Santoro, M. M. ROS homeostasis and metabolism: a dangerous liason in cancer cells. *Cell Death Dis.*, 2016; *7*(6): e2253. DOI: 10.1038/cddis.2016.105.
36. Fadaka, A., Ajiboye, B., Ojo, O., Adewale, O., Olayide, I., Emuowhochere, R. Biology of glucose metabolization in cancer cells. *J Oncol Sci.*, 2017; *3:* 45-51. DOI: https://doi.org/10.1016/j.jons.2017.06.002.
37. Pliszka, M.; Szablewski, L. Glucose Transporters as a Target for Anticancer Therapy. *Cancers (Basel)*, 2021: *13*(16). DOI: 10.3390/cancers13164184.
38. Eagle, H. Nutrition needs of mammalian cells in tissue culture. *Science*, 1955; *122*(3168): 501-514. DOI: 10.1126/science.122.3168.501.
39. Yang, L.; Venneti, S.; Nagrath, D. Glutaminolysis: A Hallmark of Cancer Metabolism. *Annu Rev Biomed Eng.*, 2017; *19:* 163-194. DOI: 10.1146/annurev-bioeng-071516-044546.
40. Thiruvalluvan, M.; Billet, S.; Bhowmick, N. A. Antagonizing Glutamine Bioavailability Promotes Radiation Sensitivity in Prostate Cancer. *Cancers (Basel)*, 2022; *14*(10). DOI: 10.3390/cancers14102491.
41. Li, D.; Fu, Z.; Chen, R.; Zhao, X.; Zhou, Y.; Zeng, B.; Yu, M.; Zhou, Q.; Lin, Q.; Gao, W.; et al. Inhibition of glutamine metabolism counteracts pancreatic cancer stem cell features and sensitizes cells to radiotherapy. *Oncotarget*, 2015; *6*(31): 31151-31163. DOI: 10.18632/oncotarget.5150 From NLM Medline.
42. Yun, J.; Mullarky, E.; Lu, C.; Bosch, K. N.; Kavalier, A.; Rivera, K.; Roper, J.; Chio, II; Giannopoulou, E. G.; Rago, C.; et al. Vitamin C selectively kills KRAS and BRAF mutant colorectal cancer cells by targeting GAPDH. *Science*, 2015; *350*(6266): 1391-1396. DOI: 10.1126/science.aaa5004.
43. Vuyyuri, S. B.; Rinkinen, J.; Worden, E.; Shim, H.; Lee, S.; Davis, K. R. Ascorbic acid and a cytostatic inhibitor of glycolysis synergistically induce apoptosis in non-small cell lung cancer cells. *PLoS One*, 2013; *8*(6): e67081. DOI: 10.1371/journal.pone.0067081.
44. El Halabi, I.; Bejjany, R.; Nasr, R.; Mukherji, D.; Temraz, S.; Nassar, F. J.; El Darsa, H.; Shamseddine, A. Ascorbic Acid in Colon Cancer: From the Basic to the Clinical Applications. *Int J Mol Sci.*, 2018; *19*(9). DOI: 10.3390/ijms19092752.
45. 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): 1425-1435. DOI: 10.4161/cbt.22003.
46. 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:* 123-130. DOI: 10.1016/j.lfs.2018.07.027.
47. 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): 1784-1795. DOI: 10.1016/j.yexcr.2013.05.001.
48. Jung, K. H.; Lee, J. H.; Park, J. W.; Quach, C. H. T.; Moon, S. H.; Cho, Y. S.; Lee, K. H. Resveratrol-loaded polymeric nanoparticles suppress glucose metabolism and tumor growth in vitro and in vivo. *Int J Pharm.*, 2015; *478*(1): 251-257. DOI: 10.1016/j.ijpharm.2014.11.049.
49. Kueck, A.; Opipari, A. W., Jr.; Griffith, K. A.; Tan, L.; Choi, M.; Huang, J.; Wahl, H.; Liu, J. R. Resveratrol inhibits glucose metabolism in human ovarian cancer cells. *Gynecol Oncol*, 2007; *107*(3): 450-457. DOI: 10.1016/j.ygyno.2007.07.065.
50. Jung, K. H.; Lee, J. H.; Thien Quach, C. H.; Paik, J. Y.; Oh, H.; Park, J. W.; Lee, E. J.; Moon, S. H.; Lee, K. H. Resveratrol suppresses cancer cell glucose uptake by targeting reactive oxygen species-mediated hypoxia-inducible factor-1alpha activation. *J Nucl Med.*, 2013; *54*(12): 2161-2167. DOI: 10.2967/jnumed.112.115436 From NLM Medline.
51. Siddiqui, F. A.; Prakasam, G.; Chattopadhyay, S.; Rehman, A. U.; Padder, R. A.; Ansari, M. A.; Irshad, R.; Mangalhara, K.; Bamezai, R. N. K.; Husain, M.; 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. DOI: 10.1038/s41598-018-25524-3 From NLM Medline.
52. Soni, V. K.; Mehta, A.; Ratre, Y. K.; Chandra, V.; Shukla, D.; Kumar, A.; Vishvakarma, N. K. Counteracting Action of Curcumin on High Glucose-Induced Chemoresistance in Hepatic Carcinoma Cells. *Front Oncol*, 2021; *11:* 738961. DOI: 10.3389/fonc.2021.738961 From NLM PubMed-not-MEDLINE.
53. 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): 474-479. DOI: 10.5483/BMBRep.2018.51.9.114.
54. Fan, W. H.; Wang, F. C.; Jin, Z.; Zhu, L.; Zhang, J. X. Curcumin Synergizes with Cisplatin to Inhibit Colon Cancer through Targeting the MicroRNA-137-Glutaminase Axis. *Curr Med Sci.*, 2022; *42*(1): 108-117. DOI: 10.1007/s11596-021-2469-0 From NLM Medline.
55. Zhou, X.; Zheng, W.; Nagana Gowda, G. A.; Raftery, D.; Donkin, S. S.; 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:* 147-156. DOI: 10.1016/j.jsbmb.2016.04.022.
56. Rojo de la Vega, M.; Chapman, E.; Zhang, D. D. NRF2 and the Hallmarks of Cancer. *Cancer Cell.*, 2018; *34*(1): 21-43. DOI: 10.1016/j.ccell.2018.03.022.
57. Ren, Z.; He, Y.; Yang, Q.; Guo, J.; Huang, H.; Li, B.; Wang, D.; Yang, Z.; Tian, X. A Comprehensive Analysis of the Glutathione Peroxidase 8 (GPX8) in Human Cancer. *Front Oncol*, 2022; *12:* 812811. DOI: 10.3389/fonc.2022.812811.
58. Wong, C. C.; Yu, J. Gut microbiota in colorectal cancer development and therapy. *Nat Rev Clin Oncol*, 2023; *20*(7): 429-452. DOI: 10.1038/s41571-023-00766-x.
59. Xu, N.; Wang, L.; Li, C.; Ding, C.; Li, C.; Fan, W.; Cheng, C.; Gu, B. Microbiota dysbiosis in lung cancer: evidence of association and potential mechanisms. *Transl Lung Cancer Res.*, 2020; *9*(4): 1554-1568. DOI: 10.21037/tlcr-20-156.
60. Zhang, J.; Xie, Q.; Huo, X.; Liu, Z.; Da, M.; Yuan, M.; Zhao, Y.; Shen, G. Impact of intestinal dysbiosis on breast cancer metastasis and progression. *Front Oncol*, 2022; *12:* 1037831. DOI: 10.3389/fonc.2022.1037831.
61. Zhong, W.; Wu, K.; Long, Z.; Zhou, X.; Zhong, C.; Wang, S.; Lai, H.; Guo, Y.; Lv, D.; Lu, J.; et al. Gut dysbiosis promotes prostate cancer progression and docetaxel resistance via activating NF-kappaB-IL6-STAT3 axis. *Microbiome*, 2022; *10*(1): 94. DOI: 10.1186/s40168-022-01289-w From NLM Medline.
62. 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; *291*(1): 84-97. DOI: 10.1111/cns.14081 From NLM Medline.
63. Maddern, A. S.; Coller, J. K.; Bowen, J. M.; Gibson, R. J. The Association between the Gut Microbiome and Development and Progression of Cancer Treatment Adverse Effects. *Cancers (Basel)*, 2023; *15*(17). DOI: 10.3390/cancers15174301 From NLM PubMed-not-MEDLINE.
64. Al-Qadami, G.; Bowen, J.; Van Sebille, Y.; Secombe, K.; Dorraki, M.; Verjans, J.; Wardill, H.; Le, H. 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. DOI: 10.1007/s00520-022-07559-5 From NLM Medline.
65. Gonzalez-Mercado, V. J.; Lim, J.; Marrero, S.; Pedro, E.; Saligan, L. N. Gut microbiota and fatigue in rectal cancer patients: a cross-sectional pilot study. *Support Care Cancer*, 2021; *29*(8): 4615-4621. DOI: 10.1007/s00520-021-06013-2 From NLM Medline.