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Review Article

Cancer Treatment with Pro and Antioxidant Agents

Sabiha Fatima

Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia

***Correspondence to:** Dr. Sabiha Fatima, Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia.

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Abstract

In almost all types of cancers mild to moderately elevated levels of reactive oxygen species (ROS) activate oncogenic signaling pathway which facilitates cancer initiation progression, invasion and metastasis. Extremely high level of ROS generated by conventional cancer therapy damages cancer cells and leads to cell death. Unfortunately, the ROS-elevating therapeutic approach not only enhance oxidative stress in cancer cells but also leads to oxidative stress induced toxicity in normal cells. In cancer ROS play a doubled-edged sword role. Therefore, to limit the undesired side effects in the normal cells and enhance oxidative stress in cancer cells dietary antioxidants have been proposed as an adjuvant in cancer therapy. Several clinical and experimental studies have shown that dietary antioxidants not only reduce the adverse effects of anticancer agents but also increase the efficacy of conventional cancer therapy. However, some evidences support that antioxidant supplements during the cancer treatments reduce the effectiveness of anticancer therapy. But till now there is no strong scientific evidence in support for or against taking antioxidant supplements during cancer treatment. Therefore, further clinical studies are needed to determine the efficacy of antioxidants in cancer therapy, their optimal doses and effectiveness in a specific cancer types.

Introduction

Chronic irritation, infection, or inflammation disturb the redox balance and may lead to pathogenesis in human. The supraphysiological levels of reactive oxygen species (ROS) in cells, particularly for prolonged periods, play a major role in many diseases, especially cancers [1]. In cancer cells continuous high levels of ROS have been detected as a result of oncogenic transformation including alteration in genetic, metabolic, and tumor microenvironment [2,3]. The ROS induced activation of cellular signaling pathways due to DNA and protein damage is considered responsible for initiation, development, progression, invasion, and metastasis of cancers [4,5]. This can be largely attributed to the enhanced activation of growth factor receptors and disruption of intracellular signaling pathways which may promote cellular proliferation by inactivation of proto-oncogenes and tumor suppressor genes, angiogenesis, and mitochondrial dysfunction contributing to cancer development [6,7]. Furthermore, the high level of ROS in cancer cells facilitates the overexpression of Nuclear factor E2-related factor 2 (Nrf2) which is involved in the regulation of antioxidant and antiapoptotic proteins [8]. Nrf2 by increasing the expression of antioxidants such as glutathione, catalase, and superoxide dismutase and antiapoptotic protein Bcl2 inhibit apoptosis and may further promote rapid growth of the cancer cells [9].

Conventional Anticancer Therapy

Ironically, the therapeutic approaches like chemotherapeutic agents, radiotherapy and photodynamic therapy used for cancer treatment increases oxidative stress to eradicate tumor cells via targeting multiple oncogenic signaling pathways. These therapeutic approaches produce high levels of ROS which induce cancer cell cycle arrest, senescence and apoptosis [10]. Antineoplastic agents also act as an inhibitor of antioxidant systems along with pro-oxidant properties to increase ROS levels in cancer cells over the threshold to toxicity level. With this regard, modestly increased ROS are oncogenic, whereas its highly enhanced levels serve as tumor suppressor [11]. Because of the double-edged sword properties of ROS in determining cell fate, cancer cells are more vulnerable to further disturbance of their redox status than normal cells. For the cancer cells with enhanced antioxidant capacity, just the ROS-elevating therapy is not sufficient. The treatment should also include the inhibition of antioxidant defense system for a successful eradication of cancer. Therefore, both pro- and antioxidant therapies have been proposed for cancer treatment.

Antioxidants in Cancer Therapy

It is well known that the redox status of the cancer cell which is under stress is different from the normal cell [12]. Normal cells maintain cellular homeostasis by the endogenous antioxidant machinery which perfectly makes redox balance between the generation and elimination of excess ROS. Unfortunately, the ROS-elevating therapeutic approaches used in cancer treatment increase the endogenous ROS threshold level in cancer cells and might also put normal cells of some organs such as kidney liver and heart vulnerable to oxidative toxicity, at risk of oxidative damage [13-15]. Therefore, current research demand is to identify the pharmacological agents which may enhance oxidative stress in cancer cells and prevent normal cells from oxidative damage.

Intensive research conducted over the last few years has shown that plant-based foods have high content of phytochemicals such as flavonoids and polyphenols with chemopreventive properties that target several key events involved in the development of cancer [16]. Several phytochemicals have shown to improve the selective killing of cancer cells in animals and cell lines. The antioxidant defense mechanism works by recognizing the cytosolic redox difference between the normal and stressed cell [17].

Phytochemicals impede tumour progression by acting directly on cancer cells or by modifying the tumour's microenvironment, creating physiologic conditions that resist tumour growth [18]. The bioactive food components such as phenethylisothiocyanate from cruciferous vegetables, curcumin from turmeric, and resveratrol from grapes have shown to possess strong pro-apoptotic activity against cells isolated from a variety of tumours. They contribute to the chemopreventive effects by directly inducing cancer cell death by apoptosis [19]. Studies have shown that epigallocatechin-3-gallate (EGCG), an abundant polyphenol found in green tea, has chemopreventive properties. It suppresses the proliferation and induces apoptosis in cancer cells [20]. EGCG has also been reported as an antiangiogenic agent that prevents the formation of new blood vessel networks required in sustaining the development of cancer by providing oxygen and nutrients to tumour cells [21,22]. In a similar manner other dietary phytochemicals such as ellagic acid, a phenolic acid found in high quantities in some fruits, such as raspberries and strawberries, and delphinidin, an anthocyanidin abundant in blueberries, also possess strong antiangiogenic property [23,24]. These phytochemicals lead to inhibition of angiogenesis by strongly inhibiting vascular endothelial growth factor receptor-2 activity and also platelet-derived growth factor receptor, found in perivascular cells [25,26]. Several plants derived bioactive compounds make tumor cells more sensitive to oxidative stress induced by radiotherapy and chemotherapy by blocking the antioxidant defense in cancer cells. Phytochemicals such as biochanin A, curcumin, and ellagic acid have been reported to play a vital role in selective killing of cancer cells in radiotherapy [27]. Curcumin, EGCG and resveratrol, the dietary polyphenols, has been shown to sensitize cancer cells to chemotherapeutic drugs [28]. It is reported that high doses of dietary antioxidant may increase the efficacy of anticancer therapy and protect the normal cells from therapy induced side effects [29]. Moreover, many *in vitro* and *in vivo* studies have shown that anti-cancer efficacy and scope of polyphenol action can be further enhanced by combining two or three polyphenols synergistically with chemically similar or different compounds [30,31].

Although, several *in vivo* studies and randomized control trials have reported that the combination of certain chemotherapeutic drugs and phytochemicals could synergistically enhance treatment efficacy and reduce the adverse side effects of anticancer drugs and may enhance the health status in cancer patients. There is still considerable controversy as to whether ROS modulation by antioxidant supplementation is clinically beneficial or detrimental for cancer treatment. Hence, targeting ROS by antioxidants not surprisingly has yielded mixed results in cancer treatment. It is likely that intake of antioxidants during cancer treatment is beneficial for some people, yet harmful for others or not all the antioxidant shows beneficial effect [1,27]. Thus, more clinical cancer research studies should be done on the use of antioxidants during conventional cancer therapy and the determination of optimal doses of antioxidant for a specific cancer type.

Bibliography

1. Kumari, S., Badana, A. K., G, M. M., G, S. & Malla, R. (2018). Reactive Oxygen Species: A key Constituent in Cancer Survival. *Biomark Insights, 13*.

2. Levine, A. S., Sun, L., Tan, R., Gao, Y., Yang, L., Chen, H., Teng, Y. & Lan, L. (2017). The oxidative DNA damage response: A review of research undertaken with Tsinghua and Xiangya students at the University of Pittsburgh. *Sci China Life Sci., 60*(10), 1077-1080.

3. Semenza, G. L. (2012). Hypoxia-inducible factors in physiology and medicine. *Cell., 148*(3), 399-408.

4. Kumari, S. & Malla, R. (2015). New Insight on the Role of Plasminogen Receptor in Cancer Progression. *Cancer Growth Metastasis, 8,* 35-42.

5. Storz, P. (2005). Reactive oxygen species in tumor progression. *Front Biosci., 10,* 1881-1896.

6. Gào, X. & Schöttker, B. (2017). Reduction-oxidation pathways involved in cancer development: a systematic review of literature reviews. *Oncotarget, 8*(31), 51888-51906.

7. Witsch, E., Sela, M. & Yarden, Y. (2010). Roles for growth factors in cancer progression. *Physiology (Bethesda), 25*(2), 85-101.

8. Jaramillo, M. C. & Zhang, D. D. (2013). The emerging role of the Nrf2-Keap1 signaling pathway in cancer. *Genes Dev., 27*(20), 2179-2191.

9. Shelton, P. & Jaiswal, A. K. (2013). The transcription factor NF-E2-related factor 2 (Nrf2): a protooncogene? *FASEB J., 27,* 414-423.

10. Trachootham, D., Alexandre, J. & Huang, P. (2009). Targeting cancer cells by ROS-mediated mechanisms: a radical therapeutic approach? *Nat Rev Drug Discov., 8,* 579-591.

11. Dho, S. H., Kim, J. Y., Kwon, E. S., Lim, J. C., Park, S. S. & Kwon, K. S. (2015). NOX5-L can stimulate proliferation and apoptosis depending on its levels and cellular context, determining cancer cell susceptibility to cisplatin. *Oncotarget, 6*(36), 39235-39246.

12. Sandhya, T., Lathika, K. M., Pandey, B. N., Bhilwade, H. N., Chaubey, R. C., Priyadarsini, K. I., *et al.* (2006). Protection against radiation oxidative damage in mice by Triphala. *Mutat Res., 609*(1), 17-25.

13. Dong, J. & Chen, H. (2018). Cardiotoxicity of Anticancer Therapeutics. *Front Cardiovas Med., 5,* 9.

14. Malyszko, J., Kozlowska, K., Kozlowski, L. & Malyszko, J. (2017). Nephrotoxicity of anticancer treatment. *Nephrol Dial Transplant, 32*(6), 924-936.

15. Vincenzi, B., Armento, G., SpalatoCeruso, M., Catania, G., Leakos, M., Santini, D., Minotti, G. & Tonini, G. (2016). Drug-induced hepatotoxicity in cancer patients - implication for treatment. *Expert Opin Drug Saf., 15*(9), 1219-1238.

16. Singh, K., Bhori, M., Kasu, Y. A., Bhat, G. & Marar, T. (2018). Antioxidants as a precious weapons in war against cancer chemotherapy inducedtoxicity - Exploring the armoury of obscurity. *Saudi Pharm J., 26*(2), 177-190.

17. Kapinova, A., Stefanicka, P., Kubatka, P., Zubor, P., Uramova, S., Kello, M., *et al.* (2017). Are plant-based functional foods better choice against cancer than single phytochemicals? A critical review of current breast cancer research. *Biomed Pharmacother., 96,* 1465-1477.

18. Russo, M., Spagnuolo, C., Tedesco, I. & Russo, G. L. (2010). Phytochemicals in cancer prevention and therapy: truth or dare? *Toxins (Basel), 2*(4), 517-551.

19. Wang, H., Khor, T. O., Shu, L., Su, Z. Y, Fuentes, F., Lee, J. H. & Kong, A. N. (2012). Plants vs. cancer: a review on natural phytochemicals in preventing and treating cancer and their druggability. *Anticancer Agents Med Chem., 12*(10), 1281-1305.

20. Cao, J., Han, J., Xiao, H., Qiao, J. & Han, M. (2016). Effect of Tea poly phenol compounds on anticancer Drugs in Terms of Anti-Tumor activity, Toxicology and Pharmacokinetics. *Nutrients, 8*(12), 762.

21. Gu, J. W., Makey, K. L., Tucker, K. B., Chinchar, E., Mao, X., Pei, I., Thomas, E. Y. & Miele, L. (2013). EGCG, a major green tea catechin suppresses breast tumor angiogenesis and growth via inhibiting the activation of HIF-1α and NFκB, and VEGF expression. *Vasc. Cell., 5*(1), 9.

22. Li, X., Feng, Y., Liu, J., Feng, X., Zhou, K. & Tang X. (2013). Epigallocatechin-3-gallate inhibits IGF-I-stimulated lung cancer angiogenesis through downregulation of HIF-1α and VEGF expression. *J. Nutr. Nutr., 6*(3), 169-178.

23. Kristo, A. S., Klimis-Zacas, D. & Sikalidis, A. K. (2016). Protective Role of Dietary Berries in Cancer. *Antioxidants (Basel), 5*(4).

24. Wang, N., Wang, Z. Y., Mo, S. L., Loo, T. Y., Wang, D. M., Luo, H. B., *et al.* (2012). Ellagic acid, a phenolic compound, exerts anti-angiogenesis effects via VEGFR-2signaling pathway in breast cancer. *Breast Cancer Res Treat., 134*(3), 943-955.

25. Lamy, S., Blanchette, M., Michaud-Levesque, J., Lafleur, R., Durocher, Y., Moghrabi, A., *et al.* (2006). Delphinidin, a dietary anthocyanidin, inhibits vascular endothelial growth factor receptor-2 phosphorylation. *Carcinogenesis, 27*(5), 989-996.

26. Sun, Q., Heilmann, J. & König, B. (2015). Natural phenolicmetabolite with anti-angiogenic properties-a review from the chemical point of view. *Beilstein J Org Chem., 11,* 249-264.

27. Prasad, N. R., Muthusamy, G., Shanmugam, M. & Ambudkar, S. V. (2016). South Asian Medicinal Compounds as Modulators to Chemotherapy and Radiotherapy. *Cancers (Basel), 8*(3), pii: E32.

28. De Oliveira Júnior, R. G., Christiane Adrielly, A. F., Da Silva Almeida, J. R. G., Grougnet, R., Thiéry, V. & Picot, L. (2018). Sensitization of tumor cells to chemotherapy by natural products: A systematic review of preclinical data and molecular mechanisms. *Fitoterapia, 129,* 383-400.

29. Prasad, K. N., Cole, W. C., Kumar, B. & Che Prasad, K. (2002). Pros and cons of antioxidant use during radiation therapy. *Cancer Treat Rev., 28*(2), 79-91.

30. Niedzwiecki, A., Roomi, M. W., Kalinovsky, T. & Rath, M. (2016). Anticancer Efficacy of Polyphenols and Their Combinations. *Nutrients, 8*(9), pii: E552.

31. Jaramillo, M. C. & Zhang, D. D. (2013). The emerging role of the Nrf2-Keap1 signaling pathway in cancer. *Genes Dev., 27*(20), 2179-2191.