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Who Plays Dual Role in Cancerous and Normal Cells? Natural Antioxidants or Free Radicals or the Cell Environment

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In the recent years, the anticancer studies on the natural products and herbal medicines have been increased with the idea that these compounds can kill cancer cells or prevent their replication and progress. Most of the positive anticancer effects of the natural products have been claimed related to their antioxidant components. In the recent years most of studies support positive effects of natural antioxidants in many debilitating human diseases such as diabetes (Hosseini and Abdollahi, 2012), hyperprolactinemia (Hasani-Ranjbar *et al*., 2010), infertility (Momtaz and Abdollahi, 2010), or aging (Hasani-Ranjbar *et al*., 2012; Momtaz and Abdollahi, 2012) etc.

Medicinal plants produce diverse secondary metabolites, of which the most important classes are phenolic compounds characterizing by at least one aromatic ring (C6) and one or more hydroxyl groups. Antioxidant activity of phenolic compounds is due to their high tendency to chelate metals by possessing hydroxyl and carboxyl groups. The flavonoids and polyphenols can directly scavenge Reactive Oxygen Species (ROS) such as superoxide, hydrogen peroxide, hydroxyl radical, or other free radicals mainly by their ability to donate electrons or hydrogen atoms. Therefore, reduced forms of phenolic compounds or some vitamins such as A, C and E act as antioxidant, but phenoxyl radicals (the oxidized form) can cause cytotoxicity especially via prolonging the lifetime of the radicals by spin-stabilization. The phenoxyl radicals are generally toxic to living systems, by initiating free-radical chain reactions in the membrane (Michalak, 2006). Thus, it can be imagined that antioxidants play dual role in treatment and prevention of cancer (Abdollahi and Shetab-Boushehri, 2012). This may be due to the dual role of ROS in cancer, because the high levels of which are either essential for cancer development or making them susceptible to ROS-induced cell death in comparison to normal cells (Lopez-Lazaro, 2007).

Interestingly, a mode of action for some anticancer drugs involves the generation of free radicals to cause cellular damage and necrosis of malignant cells. A concern has gradually developed as "How can antioxidant compounds reduce the beneficial effect of chemotherapy on malignant cells?" As for instance, antioxidants are able to interfere with the oxidative mechanisms of alkylating agents, which cause DNA damage and cell necrosis. It is notable that chemotherapy damages are usually created by sort of other mechanisms toward apoptosis. Hence, the argument that antioxidants are likely to interfere with most chemotherapies cannot be extrapolated to all drugs. Although, there are no sufficient *in vivo* evidences to confirm that vitamins E, C and A might reduce the efficacy of chemotherapy but there are reports that beta-carotenes reduce the *in vivo* effect of 5-fluorouracil on one type of tumor, and also vitamin C induces kind of resistance to doxorubicin in resistant breast cancer cells (Lamson and Brignall, 1999).

Furthermore, while many papers highlight the beneficial role of natural antioxidant in cancer prevention, several clinical trials in the 1990s in different populations brought up with different achievements such as reduction of gastric cancer cells while increasing the lung cancer cells. As a result, the other question is "How might antioxidants prevent cancer?" In fact, antioxidants wipe up free radicals, by neutralizing the electrical charges and preventing the free radicals taking electrons from other molecules. But the concern raised from this conception is by which mode of action, a natural antioxidant is able to defense normal cells against cancer inducers (http://www.cancer.gov/cancertopics/factsheet/prevention/antioxidants; Omenn *et al*., 1994).

This concept is being more complicated when one discusses about the phenolic compounds which are able to act as both antioxidant and pro-oxidant. The antioxidant activity might enhance the growth occurring in transformed cells, but undesirable pro-oxidant activity

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could damage the DNA and cellular membranes. However, cells response because of abnormal regulatory function and activity depending on extracellular and intracellular micro-oxygen environment can be different. Another challenge facing the concept is the lack of sufficient computational biology approaches to help researchers in this field.

Taking collectively, the main question still stands and so we recommend researchers to try doing tests in both normal and cancerous cells simultaneously to predict whether a natural antioxidant may show a beneficial or detrimental effect. To reach convincing conclusions, it is important to mention that anticancer effects of antioxidants mainly come from *in vitro* evidences while there are many challenges on reliability of such models due to use of frequently passaged cultured cells (Shetab-Boushehri and Abdollahi, 2012). Also, it is essential to consider and identify the anticancer mechanisms more than antioxidant effects for any compound that is hypothesized to be both antioxidant and anticancer. Therefore, the question of whether an antioxidant compound can be cytotoxic for cancer cells is still unanswered by current evidences.

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