A Reciprocal Relationship between Oxidative Stress, Antioxidants, and Cancer: A Review

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ABSTRACT

Oxidative stress is a defense mechanism that occurs when there is an imbalance between the production of reactive metabolites and free radicals and the antioxidants' ability to eliminate them. Reactive metabolites are free radicals referred to as oxidants or reactive oxygen species (ROS). Cells are harmed by this imbalance, which may influence the entire body. When the intra- and extracellular environmental circumstances in cells change, ROS is essential for stimulating the corresponding signaling pathways. All aspects of carcinogenesis, including prevention and treatment, are tightly associated with reactive species, particularly ROS. Numerous tumor suppressor genes and proto-oncogenes are deregulated by ROS, which also modify several cellular signaling pathways. However, most chemotherapy drugs and even radiation therapy dramatically raise the ROS concentrations in the tumor microenvironment. Antioxidants cause programmed cell death, which is used in cancer treatment; yet people receiving chemotherapy benefit from antioxidants. Nevertheless, the exact processes underlying this anticancer action remain unclear. Many studies carried out in laboratories and on animals revealed high concentrations of exogenic antioxidants, that inhibit the forms of free radical injury linked with the formation of cancer. There haven’t been many human clinical trials looking into the potential of dietary supplementation to reduce the risk of cancer development or death. Since there have been studies on the advantages and downsides of antioxidants in the treatment of cancer, several considerations need to be deemed before administering antioxidant supplements. In conclusion, little is known about the mechanism underlying antioxidant effect in cancer treatment.

Keywords: Nutritional supplements; antioxidants; anticancer agents; oxidative stress; ROS (Siriraj Med J 2024; 76: 550-556)

INTRODUCTION

A class of chemicals known as reactive species are produced as byproducts of several metabolic events that occur in eukaryotes. They are known to control the expression of numerous genes and signal transduction pathways. Oxidative stress is a persistent threat to cells, resulting from several endogenous and exogenous sources. On the other hand, persistent inflammation brought on by high levels of oxidative stress can develop into several diseases, including cancer, diabetes, neurological problems, and cardiovascular diseases. Because cancer cells proliferate and have higher metabolic rates, they require a higher redox level. By encouraging the transition from epithelial to mesenchymal tissue, invasion, proliferation, and angiogenesis, a moderate increase in ROS expression is linked to cancer stemness. Human volunteers were used to explore the effects of zinc, beta carotene, selenium, alpha tocopherol, tocopherol, and vitamin C as dietary antioxidant supplements. These investigations have produced a range of results. Certain preclinical studies have demonstrated that antioxidants boost tumor progression and metastasis. The cancer-bearing mice’s supplements improved the tumor cells’ capacity to metastasize and disseminate.

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species (ROS) are produced by endogenous sources, including respiratory chain action products in inner mitochondrion and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase nitrogen oxides (NOX) enzymes on the plasma cell membrane. The primary site of ROS in eukaryotic cells, where the majority of O2 generation occurs, are mitochondria. Therefore, this review will go over how ROS affects how antioxidants work against cancer after being administered in previous research. A tiny number of electrons from the electron transport chain escape during oxidative phosphorylation, creating superoxide radical (O2•−). By facilitating the production of internal and extracellular O2-from O2 and NADPH, NOX enzymes serve as an additional source of O2. The NOXs family, which consists of Duox1/2 and Nox1–Nox5, is typically composed of seven members, each of whom is an expert in generating a specific type of ROS. Nox-1, Nox-2, Nox-3, and Nox-5 only generate O2, but Nox-4 and Duoxes specifically produce H2O2 (hydrogen peroxide) (Fig 1).

**Origin of ROS and Its Function**

Exogenous sources such heavy metals, cigarette smoke, ozone, ionizing radiation, and medicines can create reactive oxygen species (ROS). Reactive oxygen species can be created by cigarette smoke because it contains a lot of organic particles like superoxide and nitric oxide that are considered as oxidants or free radicals. Two impacts of ozone exposure are fatty peroxidation and the recruitment of neutrophils into the pseudo stratified epithelial tissue of the airways. One of the carcinogens that is present at every stage of the carcinogenesis process is ionizing radiation. the generation of ROS from water radiolysis, which damages deoxyribonucleic acid (DNA) and causes gene mutations and cancer. Antineoplastic medications are examples of therapeutic medicines that can produce ROS. ROS are produced in large quantities by some drugs, including cisplatin and adriamycin, which harm DNA and kill cells. There was also an exogenous ROS generated by the heavy metal transition (Cd, Hg, Pb, Fe, As). These drugs enter the body through a number of different channels, where they metabolize or break down to produce free radicals. ROS can function as either beneficial or harmful species. Due to their involvement in a variety of biological processes in living things, they are an essential component. They contribute to preserving homeostasis by acting as messengers in cell signaling at a low level. On the other hand, excessive ROS production and accumulation in cells results in detrimental effects known as oxidative stress. Oxidative stress is a condition in which one side produces too many reactive oxygen species (ROS) while the other side lacks antioxidants. The balance status of prooxidant to antioxidant activities in eukaryotes is disrupted by this imbalance. Overexposure to ROS can cause oxidative damage to proteins, lipids, DNA, and cell membranes, which can hinder the proper functioning of these constituents. Lipid peroxidation, a process that damages cell membranes and lipoproteins, is brought on by an excess of hydroxyl radicals and peroxynitrite. As a result of this reaction,

![Fig 1. Targeting ROS using enzymatic antioxidants.](https://he02.tci-thaijo.org/index.php/sirirajmedj/index)
cytotoxic and mutagenic conjugated diene molecules and malondialdehyde (MDA) are produced. Furthermore, structural alterations and a decrease in enzyme function are caused by damage to the proteins. Oxidative damage to DNA can result in a variety of oxidative DNA lesions. Thus, emphysema, hemochromatosis, organ transplantation, acquired immunodeficiency syndrome, peptic ulcers, hypertension, pre-eclampsia, and neurological diseases have all been associated with oxidative stress. Moreover, lupus erythematosus, heart disease, stroke, and adult respiratory illnesses syndrome are examples of ischemia diseases.

ROS and Carcinogenesis
A normal cell can become a malignant neoplastic cell through a series of cellular and molecular alterations caused by both endogenous and exogenous stimuli during the multistage process of cancer. ROS are regarded as carcinogenic since they have been linked to the development, spread, and metastasis of cancer. Redox imbalance in cells is a typical occurrence in cancer cells as opposed to normal cells, and ROS can lead to this imbalance. It is widely acknowledged that oxidative DNA damage is the root cause of cancer growth. In this case, ROS can directly damage DNA during carcinogenic transformation. For example, they can catalyze the mutation of the altered DNA base 8-hydroxy-2'-deoxyguanosine (8-OHdG), which results in the development of tumors. Elevated ROS levels cause oxidative DNA damage, which can result in replication mistakes, base modification, base oxidation, single or double strand breaks, DNA cross-linking, and ultimately, cell malfunction and death. As a result, the altered DNA will cause genomic instability and, ultimately, cancer if it is not corrected. Increased reactive oxygen species (ROS) can alter several signaling paths and activate transcription aspects, such as nuclear kappa B factor (NF-kB) and nuclear factor erythroid 2-related factor 2 (Nrf2). This may result in altered gene expression patterns that promote the spread of cancer.

Can Antioxidants Outcompete Cancer Cells?
Antioxidants:
Chemicals known as antioxidants interact with free radicals and neutralize them to stop them from doing harm. Another name for antioxidants is “free radical scavengers”. The natural antioxidant defense system of the human body helps to both avoid and counteract oxidative stress. Antioxidants can mitigate the harmful effects of oxidants by dissolving them before their contact with biological targets. This stops highly reactive chemicals from releasing oxygen or starting chain reactions.

When a material is easily absorbed by the body, inhibits or suppresses the generation of free radicals, or chelates metals, it is considered optimally antioxidant. It should also function in the membrane and aqueous domains and positively affect gene expression.

Antioxidant Classifications:
Different classes of antioxidants are known:
§ Enzymatic and non-enzymatic antioxidant systems are two categories into which antioxidants can be divided. Superoxide dismutase (SOD), catalase, and glutathione-dependent enzymes are examples of enzymatic antioxidants. Non-enzymatic antioxidants can be further classified into nutritional and metabolic antioxidants. The body produces endogenous metabolic antioxidants, which include bilirubin, lipoic acid, coenzyme Q10, melatonin, Glutathione (GSH), arginine, and uric acid. Sources of nutritional antioxidants include exogenous dietary supplements and dietary consumption of nutrients like vitamin C, E, and polyphenols. Although consuming these substances may increase endogenous activity, they do not counteract free radicals. Endogenous antioxidants play a crucial role in preserving the best possible functioning of cells. However, the endogenous antioxidants are insufficient under some circumstances that encourage oxidative stress. Therefore, exogenous antioxidants must be provided to sustain good cellular activities.
§ Antioxidants can also be grouped based on their molecule size. The small-molecule antioxidants like glutathione (GSH), vitamin E, vitamin C, and carotenoids neutralize and eliminate ROS through a radical scavenging process. Large-molecule antioxidants such as Catalase (CAT), Superoxide dismutases (SOD), and glutathione peroxidase (GSH-Px), as well as sacrificial proteins like albumin, most probable scavenge ROS and block them from harming other fundamental proteins.
§ Antioxidants can also be categorized according to how soluble they are in lipids or water. Lipid-soluble antioxidants and water-soluble antioxidants are the two groups into which they are divided. Water-soluble antioxidants, like vitamin C, are in fluids inside the cell like the cytoplasmic matrix, while lipid-soluble antioxidants, including carotenoids, vitamin E, and lipoic acid, are basically located in plasma cell membranes.
Numerous studies have provided more and more evidence that flavonoids, including daidzein, flavanone hesperetin, and many others, have anticancer properties. These properties include modulating the activities of ROS-scavenging enzymes, cell cycle arrest, inducing apoptosis, autophagy, and suppressing the proliferation and invasiveness of cancer cells. In the hepatocellular
cancer cell line HCCSK-HEP-1, for example, daifzein induced apoptosis by upregulating and downregulating anti-apoptotic proteins Bcl-2 homologous antagonist killer (Bak). As a result, cytochrome c was released from the mitochondria, and caspases 3 and 9 were involved in the subsequent apoptotic cascade.23 Furthermore, as the paths behind this antineoplastic effect are still not entirely known, more research is required. Furthermore, similar to gallic acid, phenolic compounds have a potent anticancer effect on cancer cells. Their capacity to bring cell cycle stoppage, decrease oncogenic signaling cascades that control angiogenesis, cell proliferation, and apoptosis, change ROS levels, enhance tumor suppressor proteins like p53, and boost the facility to differentiate and convert into normal cells are the primary causes of these.24

As a possible phenolic chemical combination to be employed with cisplatin, gallic acid was chosen. Also known as 3,4,5-trihydroxybenzoic acid, gallic acid is a polyhydroxy phenolic complex that is obtained from many natural substances such as green tea, bananas, strawberries, grapes, and numerous other fruits. It is a naturally occurring molecule.25 It was discovered and extracted from plants for the first time in 1786 by Carl Wilhelm Scheele, a well-known Swedish chemist. Following his discovery, other researchers conducted additional investigations and reports on the molecule and its derivatives, which helped to clarify its features and mechanism. It has been observed that gallic acid exhibits anticancer properties in a variety of cancer cell types, including HeLa.26-28 Additionally, there are many natural plant-based sources of gallic acid. As a result, it was selected as a potential treatment for HeLa cells in conjunction with cisplatin to enhance the chemotherapeutic action of the platinum substance used to treat cancer.29,30

Many previous works have discussed antineoplastic activity in a range of tumor cells, including those from the esophagus, stomach, colon, breast, prostate, lung, and utmost notably, cervical carcinoma.10,31 Earlier studies have shown that treatment of tumor cells with gallic acid alone can induce a potent form of apoptosis, characterized by nuclear condensation, blebbing of the plasma membrane, release of cytochrome c from the mitochondria into the cytosol, and activation of caspase-3.32 Most previous studies conducted in labs and on animals demonstrated high concentrations of exogenic antioxidants, which obstruct the types of free radical damage related to the development of tumor. Human experiments were then done to explore the potential benefit of dietary supplementation in lowering the risk of cancer development or mortality. Many studies, involving case-control and cohort studies and other observational research, have been conducted to investigate the possibility of a relationship between the use of dietary antioxidant supplements and a decreased risk of cancer in humans. Overall, these studies have shown contradictory results because biases that could affect study outcomes have not been well controlled for.33 Since they may address the biases found in observational research, randomized controlled clinical trials are thought to give the best and most dependable evidence of the impacts and/or benefits of a health-correlated intervention. Human volunteers were used to study the effects of dietary antioxidant supplements containing zinc, beta carotene, selenium, alpha tocopherol, tocopherol, and vitamin C.34-37

Inclusive, the randomized controlled clinical trials yielded no clue supporting the use of dietary antioxidant supplements in the primary prevention of cancer38 whether consuming antioxidant supplements during neoplastic therapy changes the usefulness or diminishes the toxicity of medications has been the subject of numerous randomized controlled trials, some of which have involved relatively small patient numbers.39 Some studies revealed that patients receiving antioxidant supplements during cancer therapy had worse outcomes, particularly if they were smokers, even though the results of these trials were varied. Antioxidants have been shown in certain preclinical investigations to enhance the growth and metastasis of tumors in animals having tumors as well as the capacity of circulating tumor cells to spread.40-42 Some researchers complain that the usage of antioxidants must be in preventive doses which give a more beneficial effect on ROS while usage in therapeutic doses may increase ROS as illustrated in (Fig 2).43

Since oxidative stress is a well-established feature of cancer, antioxidants should be able to significantly reduce the incidence and progression of cancer.44 Even though several antioxidant therapy approaches have been investigated and some are currently in clinical trials, their effectiveness has not been determined. The following factors hinder antioxidants’ ability to fight cancer:

- Although complicated in vivo settings may alter antioxidants, most studies use pharmaceutical dosages rather than dietary ones based on in vitro investigations.44
- Antioxidants may exhibit unequal distribution among distinct tissues, and in certain instances, their limited bioavailability and bio-accessibility may impede their efficaciousness.45
- Depending on their concentration and oxygen pressure, certain antioxidants might show either pro-oxidant or antioxidant characteristics.46
These variables dictate the specific effects of the additional antioxidants. Furthermore, most chemotherapeutic medications cause oxidative stress and produce significant quantities of ROS. Antioxidant therapy for cancer patients may potentially have the opposite effect on the cell death caused by chemotherapy drugs.

As was previously mentioned, several antioxidants did not appear to work well in clinical situations. Since endogenous antioxidant enzymes or antioxidants account for the majority of antioxidant capacity, we propose that treating cancer patients with mild pro-oxidants to boost antioxidant activity may be a beneficial strategy. But further study is needed to fully understand the biochemical underpinnings of this, and long-term intervention monitoring is necessary. Developing new therapeutic drugs that may be useful in the prevention and treatment of cancer will be made easier by a better knowledge of these pathways. Thus, until further research can demonstrate the benefit of antioxidant supplements, cancer patients should take them with care.

CONCLUSION

Reactive oxygen species (ROS) excess can oxidatively damage proteins, lipids, DNA, and cell membranes, compromising their proper function. ROS overproduction during an antioxidant deficiency causes oxidative stress and upsets the equilibrium of prooxidant/antioxidant processes in living things. A small number of in vitro investigations using polyphenolic compounds produced encouraging findings about the antioxidant’s ability to slow the growth of cancer cells. However, inconsistent outcomes were obtained in other animal and laboratory experiments. Preclinical experiments recorded similar observations. Studies have shown that the proliferation of cancer cells following antioxidant treatment varies depending on a few aspects, including the type of cancer and the drugs utilized.

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