

Editorial

Cancer Chemoprevention by Natural Products: Current & Future Prospects

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Editorial

Cancer is a group of disease characterized by uncontrolled growth and spread of abnormal cells. If the spread is not controlled, it can result in death. Cancer is caused by both external (tobacco, chemicals, radiation and infectious organisms) and internal factors (inherited mutations, hormones, immune conditions and mutations that occur from metabolism). These causal factors may act together or in sequence to initiate or promote carcinogenesis. The myth that cancer affects people mostly in the developed countries is being broken by the fact that of the 10 million new cancer cases seen each year worldwide, nearly 5.5 million are in the less-developed countries.

Cancer is the second most common cause of death in the developed world, and a similar trend has also emerged in the developing countries. There are striking variations in the risk of different cancers by geographic area. Most of the international variation is due to exposure to known or suspected risk factors related to life style or environment, and provides a clear challenge to its prevention.

The process of carcinogenesis passes through multiple stages of biochemical and molecular alterations in target cells. Carcinogenesis involves the stepwise accumulation of genetic changes, ultimately leading to malignancy. The three main steps in multistage carcinogenesis are (1) initiation, which involves free radicals, induced genetic changes. (2) a much slower stage of carcinogenesis is promotion, which is believed to involve selective and sustained hyperplasia, leading to the specific expansion of initiated cells into papillomas, and (3) tumor progression, characterized by a high level of genetic instability that lead to chromosomal alterations.

The damaging effects of free radicals which induce cancer can be reduced by the natural or synthetic antioxidants. Antioxidants can terminate the free radicals chain reaction by donating hydrogen ions or electrons to free radicals and converting them to more stable products. Thus, antioxidants may either delay or inhibit the initiation step of carcinogenesis or can reverse the promotional stage by acting as anti promoter or growth inhibitors or by the induction of apoptosis.

Cancer chemoprevention is an important strategy to reduce the cancer burden. It has the use of natural, synthetic, or biologic chemical agents to reverse, suppress, or prevent carcinogenic progression. Recent events suggest that the new emphasis in the development of medical treatment of human diseases will be intimately connected to natural products. The use of natural products and nutraceuticals in modern medicine for the prevention or treatment of cancer is an important aspect.

Laboratory studies and epidemiological evidence lead credence to chemoprevention strategy in attenuating the risk of developing cancer in human beings. Many nutrient and non-nutrient dietary constituents of plant origin have evidence of chemoprevention by inhibiting and/or suppressing or reversing cancer incidence trend evoked by multitude of factors including environmental chemical carcinogens. Substantial epidemiological data on population indicate an association between many human cancers and lifestyle or diet. Moreover, detailed studies

of mutational events in human cancers have provided evidence for a direct action of environmental carcinogens in the development of certain cancers. This loss of genetic integrity may result due to several cumulative factors including exposure to harmful UV-radiation, potent mutagens and carcinogens, like genotoxic polyaromatic hydrocarbons (PAH), in humans and in experimental animal models. Therefore, a new science of chemoprevention has appeared as an attractive alternative to control malignancy.

Plants have been utilized since time immemorial for curing various diseases. Herbal medicine is still the mainstay of about 75-80% of the world population, mainly in the developing countries for primary health care due to better cultural acceptability, better efficacy, better compatibility with the human body and lesser side effects. Fortunately, many plant derived antioxidant nutrients and phytochemicals have the advantage of low toxicity, therapeutic potential and are protective when administered at pharmacological doses. Therefore, screening of natural products and phytochemicals presents a major avenue for the discovery of new chemopreventive drugs.

A large number of such natural compounds have been identified as having some potential cancer chemo preventive value, inhibiting mutagenesis, hyper proliferation or induce apoptosis or differentiation, which are critical characteristics of chemoprevention. Such natural agents have clear practical advantages with regard to availability, suitability for oral application, regulatory approval and mechanism of action. Substances such as phytochemicals present in food and their derivatives have been identified by a combination of constituents include vitamin derivatives, phenolics and flavanoids agents, organic sulfur compounds, isothiocyanates, curcumins, fatty acids, saponins and tannins, terpenes, alkaloids and d-limonene.

Reactive oxygen species have been implicated in premature skin aging, carcinogenesis, DNA damage, activation of signal transduction pathways related to growth differentiation and cell death; it is assumed that antioxidants could act as potential anticarcinogens at multiple stages of skin carcinogenesis. Biological systems have well developed efficient and widely distributed defensive enzyme system, which includes glutathione S transferase (GST), glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase (CAT) that can eliminate and/or detoxify the free radicals.

Biotransformation enzymes such as cytochrome P450 (CYP) isozymes are essential for initiating conversion of lipophilic xenobiotics

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into more hydrophilic, water-soluble metabolites. At the same time, induction of phase I enzymes are considered a potential cancer risk factor due to the activation of carcinogens to ultimate carcinogens. Induction/ inhibition of phase I system is assessed by the corresponding induction/inhibition of cytochrome P450 enzyme which is the major component of cytochrome P450 system. The other components of this system viz. cytochrome b5, cytochrome P450 reductase, and cytochrome b5 reductase function in a synergistic manner, facilitating the transfer of an electron to cytochrome P450 accepted from NADPH or NADH, thus enabling the proper functioning of the cytochrome P450 system.

Induction of phase II enzymes is an important mechanism of chemoprevention. Glutathione-S-transferase and DT-diaphorase are considered to be the major phase II enzymes. Glutathione-S-transferase is a multigene family of isoenzymes that catalyze the conjugation of glutathione (GSH) to a variety of electrophilic compounds as the first step in a detoxification pathway leading to mercapturic acid formation.

Glutathione, often regarded as the first line of defense against oxidative stress, is the most important cellular thiol that acts as a substrate for several transferases, peroxidases and other enzymes which prevent or mitigate the deleterious effects of oxygen free radicals.

Vitamin C is necessary for the recycling of glutathione and is an effective quencher of reactive oxygen species. Number of laboratory studies has shown the pronounced effect of vitamin C in decreasing the incidence and delaying the onset of malignant tumors in murine photocarcinogenesis models.

Many herbs and spices are known to possess an array of biochemical and pharmacological activities including antioxidant and anti-inflammatory properties that are believed to contribute to their anticarcinogenic and antimutagenic activities. Since tumor promotion is closely linked to inflammation and oxidative stress, a compound that exhibits anti inflammatory and/or antioxidant properties could act as anticarcinogenic agent.

The natural products or compounds from various natural herbs are potential candidates for development of chemo preventive and chemo-therapeutic agents against cancer. Understanding the molecular mechanism of action of these natural products and their effects on cellular signaling processes as well as their structure-activity relationships are necessary for the development of new derivatives with more favorable profile in antiproliferative and chemo preventive activities. Additional mechanism-based preventive approaches as secondary line of defense are urgently required for prevention and management of cancer.

Concepts and methods that have developed in the field of cellular and molecular biology will accelerate this progress. Indeed, we are currently in a very exciting phase of cancer research that brings together fields of cancer research which in the past were often disparate and disconnected, i.e. basic laboratory studies, epidemiology, prevention and treatment. Thus, the astounding advances in our understanding of the molecular biology of cancer provide a unified concept of the nature of the cancer cells and also suggest new clinical approaches to cancer etiology, prevention and treatment.

Many of the biomarkers being developed for etiological studies, using the approach of molecular epidemiology, can also serve as biomarkers or intermediate end points to evaluate the efficacy of dietary intervention and chemoprevention studies. Some of these biomarkers will also be useful for evaluating the efficacy of cancer therapy. Eventually the attention must shift to intervention protocols and these might be best realized in an international context. There is undoubtedly a great deal of interest in natural products and health foods. A number of International projects could be envisaged based on the theme of the present editorial.

Furthermore, certain compounds being developed for cancer chemoprevention may also be useful in the therapy of fully established neoplasms. It seems likely, therefore, these powerful and unifying themes will accelerate advances in both cancer prevention and treatment, thus leading to major reductions in both the incidence and mortality of human cancer.