Characterization of Natural Product Chemopreventive Agents

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1. INTRODUCTION

Cancer is a complicated group of diseases characterized by the uncontrolled growth and spread of abnormal cells (1). In 2002, 1,284,900 new cases of cancer were estimated to be diagnosed in the United States (US), and about 555,500 persons were expected to die of cancer, i.e., more than 1500 every day (2). Despite small decreases in overall cancer incidence and mortality rates in the US since the early 1990s, the total number of recorded cancer deaths continues to increase due to an aging and expanding population (2). Furthermore, deaths from certain carcinomas of the lung and bronchus, breast, prostate, and colon and rectum remain high, and 5-yr survival rates for many cancer patients are still very low: for cancers of the brain, 32%; esophagus, 14%; liver, 6%; lung and bronchus, 15%; pancreas, 4%; stomach, 22%; and multiple myeloma, 29% (2). Obviously, cancer remains a formidable public health problem.

A “war on cancer” was proclaimed about 30 yr ago. There was great hope and anticipation of reducing mortality rates for common forms of cancer by half by the year 2000 (3–6). Although this stated goal of the US National Cancer Institute (NCI), National Institutes of Health (NIH), has not been attained, much progress has been made, and basic research has further elucidated mechanisms whereby normal cells and tissues become malignant (5).
Cancer is considered the end stage of a chronic disease process characterized by abnormal cell and tissue differentiation (6). This process of carcinogenesis eventually leads to the final outcome of invasive and metastatic cancer. Recent advances in defining cellular and molecular levels of carcinogenesis, along with a growing body of experimental, epidemiological, and clinical trial data, have led to the development of cancer chemoprevention, a relatively new strategy in preventing cancer (7–10). Cancer chemoprevention is defined as the use of synthetic or natural agents to inhibit, retard, or reverse the process of carcinogenesis (7–11).

Invasive cancer derives from complex interactions of exogenous (environmental) and/or endogenous (e.g., genetic, hormonal, and immunological) factors (5,12,13). Carcinogenesis is progressive, and this progression in precancer is characterized by the appearance of specific molecular and more general genotypic damage associated with increasingly severe dysplastic phenotypes (11). The development of this phenomenon may be represented by three stages that often overlap: initiation, promotion, and progression phases (10). Initiation, an irreversible event, begins when normal cells are exposed to a carcinogen and their genomic DNA undergoes damage that remains unrepaired or misrepaired (10). Promotion, an expansion of the damaged cells, leads to the appearance of benign tumors. Progression, an irreversible process, produces a new clone of tumor cells with increased proliferative capacity, invasiveness, and metastatic potential (10). Transitions between successive stages are believed to be enhanced or suppressed by various factors (5).

Most human cancers seem to be potentially preventable because of controllable or removable causative exogenous factors, such as cigarette smoking, dietary factors, environmental and occupational chemicals, lifestyle and socioeconomic factors, radiation, and specific microorganisms (5,13). These exogenous factors offer the most likely opportunities for interventions targeted to primary prevention—that is, elimination of or avoiding exposure to these environmental factors (10). In addition, however, as a serious and practical approach to the control of cancer, cancer chemoprevention can play an integral role in the overall strategy geared toward reducing the incidence of cancer (3,6,8,14).

Cancer chemopreventive agents, based on their individual underlying mechanisms of action, may be classified into three categories: inhibitors of carcinogen formation, blocking (antiinitiation) agents, and suppressing (antiproliferation/antiprogession) agents (8,10,15–17). Many inhibitors of carcinogen formation, such as ascorbic acid (18), phenols (caffeic acid and ferulic acid) (19), sulphhydryl compounds (N-acetyl-L-cysteine) (20), and amino acids (proline and thioproline) (21), act to prevent formation of nitrosamines from secondary amines and nitrite in an acidic environment (16).

Chemoprevention strategies address four goals: inhibition of carcinogens, logical intervention for persons at genetic risk, treatment of precancerous lesions, and translation of leads from dietary epidemiology to intervention strategies (22). Rational and successful implementation of chemopreventive strategies relies intrinsically on tests for efficacy and mechanistic assays, as well as availability of promising chemopreventive agents, reliable intermediate biomarkers, and appropriate clinical cohorts to discover safe and effective drugs for primary and secondary prevention of human cancers (23). Established in the early 1980s, the NCI’s Chemoprevention Program has since evaluated more than 1000 potential chemopreventive agents or agent combinations, including more than 40 compounds in about 100 clinical trials (24). Included among a number of plant-derived natural products in this group of potential cancer chemopreventive agents are S-allyl-L-cystéine, curcumin, epigalallocatechin gallate, genistein, lycopene, perillyl alcohol, and a mixture of soy isoflavones, all of dietary origin (24). This program generally begins by identifying candidate agents through in vitro bioassay screening, epidemiology, and other scientific efforts (13,15). Once potential leads have been identified, mechanistic evaluations through additional in vitro and ex vivo assays are important to assess efficacy, and for planning further tests in animal models to design regimens for clinical testing and use (17,25,26). Agents judged to have potential as human cancer chemopreventive agents are subjected to preclinical toxicology and pharmacokinetic studies (27), followed by Phase I clinical safety and pharmacokinetic trials (28). The most successful agents subsequently progress to clinical chemoprevention trials (23,26).

A competitive cancer chemoprevention program titled “Natural Inhibitors of Carcinogenesis” (P01 CA48112) has been supported since 1991 by NCI. The overall theme, and botanical, biological, chemical, biostatistical, and administrative aspects of this program have been summarized previously (29–33). Currently, we provide an update and additional representatives of diverse classes of plant secondary metabolites associated with biological activity in preliminary in vitro assays, with some of these having