BIOCHEMICAL PHARMACOLOGY 74 (2007) 533–544

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/biochempharm

Commentary

Ins and outs of dietary phytochemicals in cancer chemoprevention

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ARTICLE INFO

Keywords:
Phytochemicals
Polyphenols
Antioxidant
Chemoprevention
Resveratrol
Quercetin
Diet

ABSTRACT

A voluminous number of evidence suggests that an increased consumption of fruit and vegetables is a relatively easy and practical strategy to reduce significantly the incidence of chronic diseases, such as cancer, cardiovascular diseases and other aging-related pathologies. This review will critically discuss the applications of chemical and dietary chemoprevention, intending the protecting effects against cancer of chemically synthesized molecules, or phytochemicals present in the regular diet. The length of chemopreventive treatments requires the administration of low doses of chemopreventive agents, to avoid toxic side effects. This poses the question, here discussed, of the bioavailability of these compounds, usually very modest. Another key issue is whether purified phytochemicals have the same protective effects, as do the whole food or mixture of foods in which these compounds are present. These aspects will be analysed at the light of the ''antioxidant hypothesis'' in cancer prevention and the ''combination chemoprevention'', both referring to the pleiotropic and synergistic effects of compounds present in the diet. Single molecules may evolve in perfect chemopreventive agents, as in the case of tamoxifen, or generate ambiguity. Resveratrol and quercetin represent two paradoxes, discussed here.

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1. Introduction

According to the recent 29th report on the health status of the United States, the overall rate for leading causes of death for all ages between 1950 and 2002 substantially decreased [1]. This important result is primarily due to the significant reduction of deaths for stroke and heart diseases starting from the seventies (in 2002 the age-adjusted death rate for heart diseases was 59% lower than in 1950). On the opposite, the overall rates for cancer, the second leading cause of death throughout the same period, has not been so positive. Cancer mortality rose between 1960 and 1990 and then reversed direction very slowly through 2003 for all races and both sexes combined [1,2]. Female lung cancer incidence rate increased from 1975 to 2003, decelerating since 1991, while breast cancer stabilized from 2001 to 2003 [2]. According to other studies, several common forms of epithelial malignancies (e.g., lung, colorectal, prostate, pancreas, breast and ovary), for both sexes, showed a negative trends in the last 30 years [3]. These statistical and epidemiological data provide the rationale to implement cancer prevention programmes.

According to a seminal paper published in 1981 and based on epidemiological studies, an average of 35% of overall human death rate for cancer is associated to nutritional

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0006-2952/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.bcp.2007.02.014

factors [4]. This hypothesis, re-evaluated at the light of compelling evidence on an inverse relationship between fruits and vegetables consumption and risk of cancer [5], has two rational explanations: (i) the presence in the diet of suspected carcinogens; (ii) the absence in the diet of compounds possessing cancer preventing (chemopreventive) properties. Starting from the early 1980s, in United States, several governmental agencies promoted programmes on cancer prevention that had considerably grown since then.[1] Dietary guidelines have been established in order to reduce the risk of cancer. Actually, several hundreds molecules are studied as potential ''chemopreventive agents'', and over 50 compounds are being tested in clinical trials [6]. Despite these enormous efforts, chemoprevention represents a highly controversial topic due to ethical, economic and scientific issues.

This review will focus on some key aspects of cancer chemoprevention, including bioavailability and pleiotropy of potential chemopreventive agents. Differences existing between dietary and pharmacological forms of chemoprevention will be discussed.

2. *Chemoprevention*: what does it mean? An historical perspective

When, Dr. Michael Sporn coined for the first time the term ''chemoprevention'', referring to the activity of natural forms of vitamin A in preventing the development and progression of epithelial cancer [7], he originated a novel field in cancer research. Accordingly to a more modern and complete definition, chemoprevention includes the use of natural or pharmacological agents to suppress, arrest or reverse carcinogenesis, at its *early* stages [3]. The term ''chemoprevention'', passed from 4000 to 10,000 citations in PubMed in the last quinquennium, is now broadly used to indicate the ability of a molecule not only to prevent, but also to cure cancer. In other cases, the attribute ''chemopreventive'' has been associated to a life style, such as a correct diet. As a consequence, ''chemopreventive'' effects are largely described in the current Literature and result from a plethora of different experimental approaches: epidemiological studies on human subjects; clinical trials on patients; studies on animal models where carcinogenesis was experimentally induced; *in vitro* tests on cell lines.

Following the indications of the National Cancer Institute (NCI), five classes of chemopreventive agents show promising results in clinic, and are considered of high priority: selective estrogen receptor modulator (SERMs); non-steroidal anti-inflammatory drug (NSAIDs); calcium compounds; glucocorticoids; retinoids.[1] Many of these compounds are chemically synthesized and have already been applied in pharmacological therapies to cure diseases different from cancer, before their use as chemopreventive drugs. In parallel, the NCI, based on numerous reports describing the anticancer activity of naturally occurring molecules [8,9], identified about 40 edible plants possessing potential chemopreventive compounds, globally known as phytochemicals. However, in many cases, the chemopreventive effects of these compounds are primarily based on cell culture and animal model studies, and only few of them are entering clinical trials [6] (Table 1). Therefore, from a functional, pharmacological and clinical point of view, it would be useful to distinguish between ''pharmacological'' and ''dietary'' chemoprevention.

For the purpose of this review, I will use the term ''phytochemicals'' to indicate the following classes of non-nutrient compounds present in fruit and vegetables: carotenoids, polyphenols, alkaloids, nitrogen-containing and organosulfur compounds. Together with carotenoids, polyphenols represent the most studied class of phytochemicals. They includes the following sub-groups: phenolic acid, tannins, stilbenes, coumarins and flavonoids (reviewed in [10]). Most of these compounds possess strong antioxidant properties that contributed to formulate the ''antioxidant hypothesis'' in cancer prevention.

3. ''Pharmacological'' chemoprevention

Actually, the concept of ''multistep carcinogenesis'' proposes that cancer generates over a period of time due to the accumulation of somatic mutations in a single cell, resulting in gradual phenotypic changes, from a normal to a pre-neoplastic cell, that progresses to neoplastic [9,11]. These different stages in carcinogenesis are generally described as: initiation (days), promotion (several years), and progression (1–5 years). Initiation is irreversible and includes the initial hit by chemical or physical carcinogenic agents directly at DNA level. Promotion, which involves epigenetic mechanisms, is usually a relatively slow and reversible process leading to accumulation of pre-malignant cells abnormally dividing. Progression is generally irreversible, and leads to the final stage of carcinogenesis with tumor growth and acquisition of invasiveness and metastatic potential [9,11]. Excellent animal models and transgenic mice have been established to study multistep carcinogenesis for breast, prostate, colon, lung cancer [11–13]. The passage from pre-malignant to malignant cell involves activation of proto-oncogenes and/or inactivation of tumor suppressor genes (reviewed in [11]). Both categories of genes, when mutated, cause alterations in key cellular processes linked to cell growth and proliferation. A good chemopreventive agent should be able to interfere with one or more phases of the multistep carcinogenesis process.

The efficacy of a novel chemopreventive agent is measured throughout the same procedures applied to a new drug. It must satisfy the following requirements: (1) primary prevention in high risk healthy individuals; (2) cancer prevention in individuals that already had developed pre-malignant lesions; (3) prevention of secondary forms of cancers in patients already treated for a primary cancer [14,15]. The final endpoint of all three aspects of chemoprevention is the attainment of clinical evidence for cancer reduction.

During the past two decades, NCI established a system for a scientific approach to developing chemopreventive agents starting from epidemiological and basic laboratory data, and ending with stepwise clinical trials. These procedures finally led the Food and Drug Administration (FDA) to apply chemoprevention to human subjects [14,15]. Preclinical

[1] http://www3.cancer.gov/prevention/cadrg.

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