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Review

Prenylated chalcones and flavonoids for the prevention and treatment of cancer

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ABSTRACT

Prenylated chalcones and flavonoids gained increasing attention not only in nutrition but also in cancer prevention because of their biological and molecular activities in humans, which have been extensively investigated in vitro or in preclinical studies. These naturally occurring compounds exhibit antioxidant effects, modulate metabolism of carcinogens by inhibition of distinct phase 1 metabolic enzymes and activation of phase 2 detoxifying enzymes, and display antiinflammatory properties. In particular, their potential to prevent proliferation of tumor cells is noteworthy. Some representatives of this subclass of secondary plant compounds exert pronounced anti–tumor-initiating capacities and directly inhibit growth of cancer cells, whereas their toxic effects on healthy tissues are remarkably low. These promising pharmacologic characteristics are countered by low ingestion, low bioavailability, and little knowledge of their metabolism. This review focuses on the great potential of these plant- and nutrient-derived compounds for cancer prevention and therapy. Provided here is a comprehensive summary of the current knowledge and inherent modes of action, focusing on the prenylated chalcones xanthohumol, desmethylxanthohumol, and xanthogalenol, as well as the prenylated flavonoids isoxanthohumol, 6-prenylnaringenin, 8-prenylnaringenin, 6-geranylnaringenin, 8-geranylnaringenin, and pomiferin.

Introduction

Globally, cancer constitutes a tremendous health problem. Annually it causes more than 7 million deaths; approximately 10 million people are newly diagnosed with cancer each year, and this number continues to increase [1,2]. Despite recent therapeutic breakthroughs that prolong overall survival for certain types of cancer [3–5], the progress in cancer therapy achieved in the past 30 y disappointingly did not significantly lower the mortality rate on a global scale [2]. The relative incidence estimations of the 10 major cancer entities for the United States in the year 2014 are illustrated in Figure 1 [6]. More than 1,600,000 new cancer cases are expected for the United States only, according to incidence data obtained from the National Cancer Institute, Centers for Disease Control and Prevention, and North American Association of Central Cancer Registries [6].

In contrast to benign tumors, malignant tumors invade adjacent tissues and metastasize to distant organs. Thus, cancer denotes a malignant neoplasia with deregulated and increased cell proliferation and uncontrolled cellular invasive migration. More than 100 different types of human cancers are known [7]. The underlying reasons for cancer development are complex and only partially understood. According to current estimates, only 5% to 10% of all cancer cases are caused directly by genetic defects like gain-of-function mutations in oncogenes, loss-of-function mutations in tumor suppressor genes, and mutations in the DNA repair system [1,7]. Essential factors, which can cause or promote carcinogenesis, are related to environment and lifestyle, such as tobacco use, excessive alcohol consumption, accumulated exposure to ultraviolet light, little physical activity, and unhealthy diets [1]. On the cellular level the transformation of a

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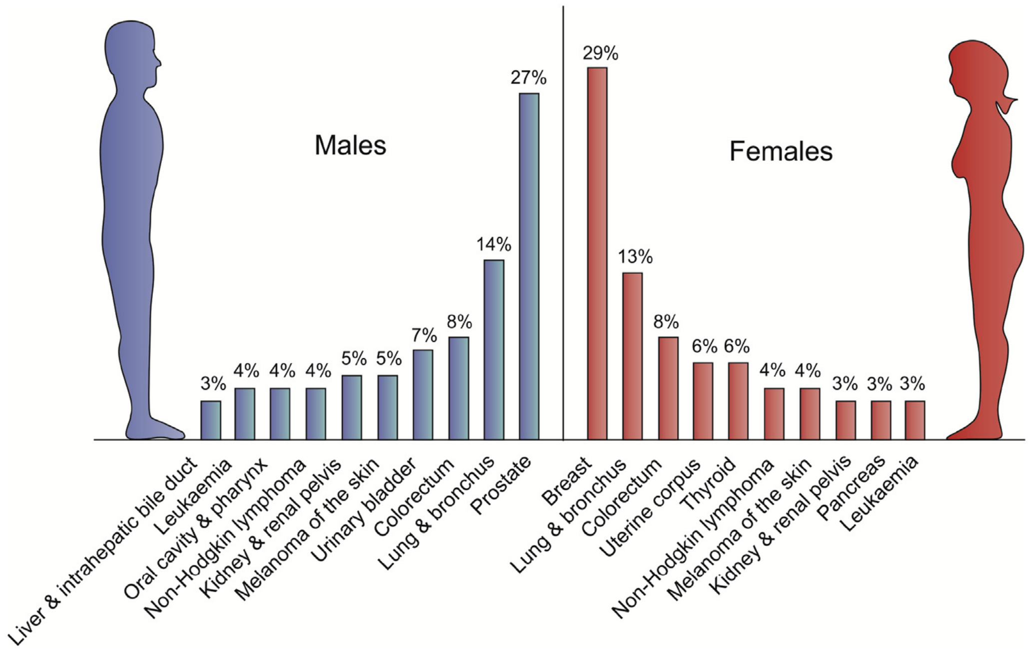

Fig. 1. Incidence of the 10 major cancer types in the United States 2014. Red bars: women; blue bars: men. Modified from Siegel et al. [6].

benign into a cancer cell requires a number of consecutive steps that ultimately lead to limitless, uncontrolled proliferation and invasive migration [7,8]. Even though cancer cells share some characteristics, they are very different because of their embryonic origin and degree of differentiation. It is widely recognized that the following six cellular alterations are necessary to enable malignant growth: 1) independence of growth signals, 2) insensitivity to growth-inhibitory signals, 3) escape from physiologic apoptosis, 4) limitless proliferative potential, (5) persistent angiogenesis, and 6) tissue invasion enabling metastasis [7]. The necessity for all six preconditions is one explanation why despite its increasing incidence, cancer is generally not an inevitable disease during an average human lifetime [7].

Nutrition plays a crucial role in the development and prevention of cancer. In particular, phytochemicals, minor compounds present in plants and thus in plant food, are intensively investigated with respect to both their contribution to and inhibition of cancer formation [9,10]. Because of their interesting and important biological activities, the pharmacologic properties of prenylated flavonoids found in hops have been described and summarized previously [11–14].

Occurrence and classification of prenylated chalcones and flavonoids

Flavonoids are one of the largest groups of secondary plant metabolites and are widely distributed in plant foods. The basic structural feature of all flavonoids is the flavane (2- phenyl-benzo-γ-pyrane) nucleus, a system of two benzene rings (A and B) linked by an oxygen-containing pyrane ring (C ring) [15,16]. Chalcones, a subclass of flavonoids according to the new classification of polyphenols (Phenol-Explorer Version 3.6 database, www.phenol-explorer.eu), possess an open C-ring system. Prenylated chalcones and flavonoids or prenylflavonoids possess one or more prenyl groups covalently bound to the flavonoid backbone (Fig. 2). These prenylated substances are produced by only a limited number of plant families, mainly Asclepiadaceae, Asteraceae, Berberidaceae, Cannabacea, Clusiaceae, Fabaceae, Leguminosae, Moraceae, Platanaceae, Ptaeroxylaceae, Rutaceae, Sapindaceae, and Scrophulariacea. Selected plant-derived derivatives with their respective origins are listed in Table 1 [14, 17–23]. About 80% of the approximately 1100 known prenylated flavonoids are found in the three plant families Asteraceae, Cannabinaceae, and Leguminosae, among which the highest concentrations of prenylflavonoids are detected in *Humulus lupulus* (Cannabinaceae), better known as hops [14,24]. Depending on their chemical structure, prenylated flavonoids are divided into several subclasses, with prenylflavones, prenylflavonols, and prenylflavanones as important representatives. Generally, prenylated chalcones and flavonoids are characterized by one or more prenyl groups. With increasing numbers of prenyl groups in the molecule, 1) lipophilicity, 2) membrane attachment, and 3) transmembrane transport increase, possibly enhancing biological activity [25]. Many flavonoids have a corresponding prenylated derivative. However, comparatively little is known about their biological properties or pharmacologic activity, although in recent years increasing numbers of prenylflavonoids have been discovered and described in the literature.

The growing interest in prenylated flavonoids can be explained by the abundance of reports describing their

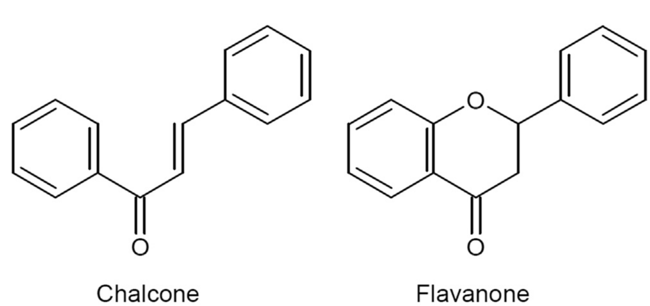

Fig. 2. Chalcones and flavonoids are closely related plant compounds. Chalcones are characterized by an open ring structure and often considered as flavonoid derivatives.