

EDITORIAL

Part I: Pharmacognosy and Molecular Pharmacology of Small Molecules of Natural Origin for Cancer Therapy and Chemoprevention

Cancer still belongs to the second-leading cause of death in industrialized countries. The fate of many cancer patients, for whom cure of their disease is not a reality, is becoming ever more of an issue. There are unprecedented efforts to uncover new treatment, and the knowledge on cancer has increased dramatically over the past four decades (Fig. 1A). Medicinal plants and other marine and terrestrial natural sources are a fertile ground to find compounds with pharmacological features.

The recent developments in drug discovery from natural resources can be traced back to fundamental observations in the first half of the 20th century. The term “allelopathy” coined by the plant physiologist Hans Molisch in 1937 describes the effect of products of a donor plant on abiotic and biotic environmental factors. In line with this term is the name “allelochemicals” coined by Whittaker and Feeny in 1971 for compounds by which organisms of one species affect the growth, health, behaviour or population biology of other species, excluding nutrients and vitamin-like compounds. Typically, allelochemicals are secondary metabolites, which are – in contrast to primary metabolites – not essential for the nutrition of plants. Secondary metabolites are regarded as defence against competitors, herbivores and pathogens and signal compounds to attract insects for reproduction. Therefore, secondary metabolites represent an important part of the plants’ life strategies to maintain survival and reproductive fitness. Fortunately, many secondary metabolites of terrestrial and marine organisms exert pharmacological features. It is, however, quite clear that the pharmacological activities of secondary metabolites does not represent an altruistic behaviour of other organisms towards humans but rather a pleasing side effect.

Although medicinal herbs gradually lost importance in the course of chemistry’s progress in industrialized countries during the 20th century, the current thriving revival of phytotherapy is followed by an increasing scientific interest in bioactive compounds as lead drugs for semi-synthetic modification. As a matter of fact, the number of biomedical publications dealing with natural products is constantly increasing in recent years (Fig. 1A). Cancer therapy and especially natural products are important topics of cancer research (Fig. 1B). A smaller, but increasing number of papers deals with the prevention of cancer.

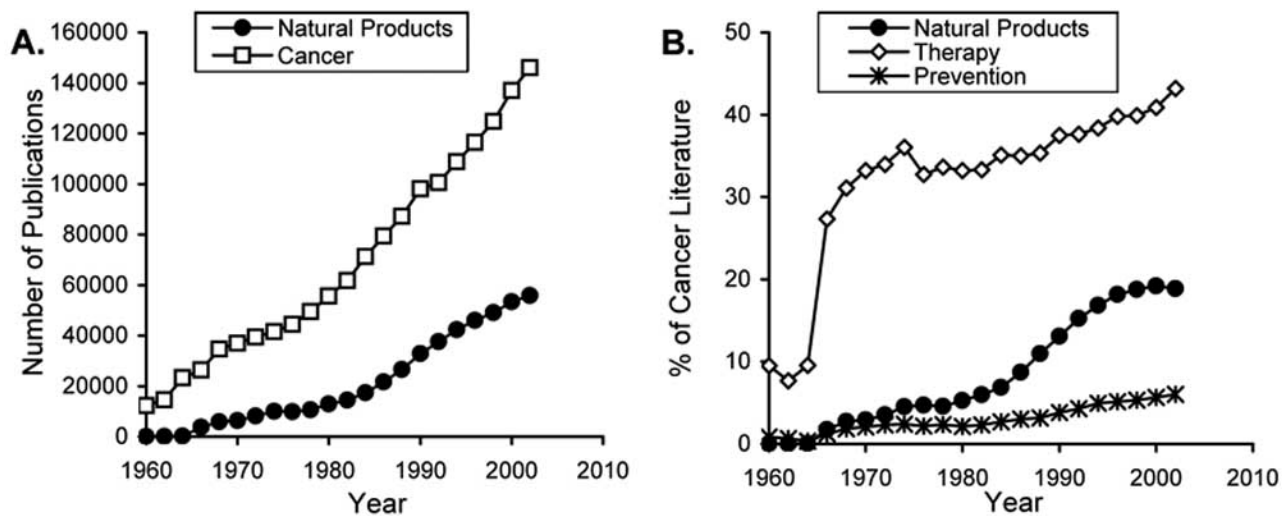


Fig. (1). Survey of literature published since 1960 on (A) cancer and natural products and (B) the proportions of papers on cancer dealing with natural products, therapy, and prevention.

It comes as no surprise that natural products belong to the major players in cancer research, since a considerable portion of anti-tumor agents currently used in the clinic are of natural origin. Drugs of different classes are part of the armatorium to fight the war against cancer, e.g., *Vinca* alkaloids (vincristine, vinblastine, vindesine, vinorelbine), taxanes (paclitaxel, docetaxel), epipodophyllotoxines (etoposide, teniposide), camptothecin and its derivatives (topotecan, irinotecan), anthracyclines (doxorubicin, daunorubicin, epirubicin, idarubicin), and others. Over the past years, there was a major shift in the development of cancer drugs, from screening of cytotoxic drugs to the development of molecularly targeted drugs. The conceptual idea is that the knowledge of the mechanism(s) of a drug provides a better approach to reach improved clinical results on the basis of patients’ molecular characteristics. The complexity of this task requires the interaction of scientists of different fields.

I was fortunate to attract a panel of reputed experts from different fields working on innovative small molecules of natural origin. Due to the broad spectrum of the subject covered their work is being presented in two separate issues of *Current Drug Target*, which appear consecutively as part **I** and **II** of the title “Small molecules of natural origin for cancer therapy and chemoprevention”. In part **I** the articles are organized in two chapters.

1. Pharmacognosy: bioactive molecules from nature

Michael Heinrich and Paul Bremner (London, UK) give a valuable introduction to ethnobotany and ethnopharmacy and their role for anti-cancer drug development. The authors span the bow from the ethnic origin of knowledge about medicinal plants to the Convention of Biological Diversity (Rio Convention) and the specific targeting of cancer-related molecules by natural products.

William P. Jones, Young-Won Chin, and A. Douglas Kinghorn (Columbus, OH, USA) emphasize the role of ethnobotany and botanical medicine to foster the identification of new drugs and discuss chances of high-throughput screenings with natural products. Semi-synthetic derivatization of natural products has a major impact for drug discovery. The authors point to chemical informatics comparisons between natural products and synthetic compounds showing that natural products have considerably higher “drug-likeness” than synthetic compounds.

It may sound as a platitude that many drugs currently used in the clinic are from natural origin. However, thinking this notion out makes clear that the biodiversity of the world provides an incredible reservoir of yet unexplored chemical structures with pharmacological features for the future. **G. Tan, C. Gyllenhaal and D.D. Soejarto** (Chicago, IL, USA) illuminate the various aspects of biodiversity for the identification and development of novel anticancer drugs.

David J. Newman and Gordon M. Cragg (Frederick, MD, USA): Natural Products) give a conceptual overview of natural products from marine invertebrates and microbes as modulators of anti-tumor targets. They give the reader an impression of how large this still poorly explored field is and which surprises scientists might be facing in the years to come. Highlighting on the most promising candidates illustrates this fascinating field of research.

2. Molecular pharmacology: inhibitors of drug targets in cancer cells

The *Vinca* alkaloids and the taxanes are well-known success stories in cancer chemotherapy. The question arises: What is new and worth reporting on this drug class? The problems with classical anti-mitotic drugs (as well as drugs of other classes) are

1. the frequent development of resistance of tumors, i.e., by multidrug resistance mediating ATP-binding cassette (ABC) transporters such as P-glycoprotein/*MDR1* and
2. the development of severe side effects, i.e., neurotoxicity.

Hence, novel antimitotic drugs are required. **Advait Nagle, Wooyoung Hur and Nathanael S. Gray** (San Diego, USA) provide a close look into this field and point out a number of exciting developments during the past few years. Apart from the classical tubulin poisons there are several non-tubulin interactors that disturb mitosis.

Over 500 tyrosine kinase genes have been identified in the human genome yet, and tyrosine kinases play an important role in cancer biology. Hence, it comes as no surprise that tyrosine kinases are exquisite targets for the identification of novel anti-cancer drugs. **Fatih M. Uckun** (St. Paul, MN, USA) reviews the current developments on inhibitors of Janus kinase 3 (JAK3) and Bruton's tyrosine kinase (BTK).

Flavonoids affect cell cycle control at different points. They are, hence, of utmost importance for cancer treatment and prevention. **Rana Pratap Singh and Rajesh Agarwal** (Denver, CO, USA) provide an overview on flavonoids and their specific targets in the deregulated cell cycle machinery of cancer cells and in apoptosis such as mitogenic signalling upstream of the cell cycle, CDKs, cyclins, p53, RB1, E2F, CDC25C, ATM, surviving and others.

As pointed out by **Dale G. Nagle and Yu-Dong Zhou** (University, MI, USA), natural inhibitors of hypoxia-inducing factor-1 are an interesting class of candidates for molecular targeted cancer therapy. Hypoxia-inducible factor-1 α (HIF1A) is a key regulator of cellular response to hypoxic stress. Among other physiological and pathological processes, HIF1A also plays a role in tumorigenesis. This makes HIF1A an attractive drug target. Nagle and Zhou report that some established cytostatic drugs of natural origin also act as inhibitors of HIF1A. Research focuses now on novel HIF1A inhibitors of natural origin with specific mechanisms of action, e.g., degradation of the HIF1A protein, prevention of HIF1A protein accumulation, or inhibition of interaction between HIF1A and co-activators.

The search for natural anti-cancer products makes only sense, if novel compounds find their way into the clinic. Translational research from the bench to the bedside is extremely important, if all these efforts should pay out for patients. After describing the pathophysiology of angiogenesis, **C.P. Neal, D.P. Berry, H. Doucas, M.M. Manson, W. Steward and Guiseppe Garcea** (Leicester, UK) systematically review the literature on clinical trials with anti-angiogenic natural products.

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