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Special Issue Editorial

Editorial: Chemoprevention of cancer by natural products

Drugs inspired by nature play an indispensable role in modern therapy. Monoclonal antibodies, immunotherapies, nucleic acid-based therapies as well as chemical drugs derived from natural resources are all based on natural origin. Chemical structures of plants (phytoalexins) and microorganisms (antibiotics) represent the result of evolutionary processes of life during millions of years to adapt to adverse environmental conditions, in order to cope with competitors for nutritional resources and to deter parasites and predators.

As repeatedly surveyed by the National Cancer Institute, USA, an astonishing high number of approved drugs used in routine treatment of cancer but also many other diseases are natural products or their semisynthetic or synthetic derivatives or are drugs based on bioactive principles discovered in nature [1,2]. Well-known showcase examples are anticancer agents from the drug classes of *Vinca* alkaloids (vincristine and vinblastine from *Catharanthus roseus* and the derivatives vindesine, vinorelbine), taxanes (paclitaxel from *Taxus brevifolia* and the semisynthetic derivative docetaxel from *Taxus baccata*), epipodophyllotoxins (etoposide and teniposide as derivatives of podophyllotoxin from *Podophyllum peltatum*), camptothecins (topotecan and irinotecan as derivatives of camptothecin from *Camptotheca accumunata*), anthracyclines (doxorubicin and daunorubicin from *Streptomyces peucetius* and the derivatives epirubicin and idarubicin), and antimetabolites (cytosine-arabinoside from the Caribbean marine sponge *Cryptotheca cripta*, 5-fluorouracil, a synthetic derivative of uracil). In addition, numerous drugs used to manage other diseases and ailments are of natural origin. Artemisinin from *Artemisia annua*, acetyl salicylic acid as synthetic derivative of salicin and saligenin from the bark of *Salix* species, verapamil as papaverine derivative from *Papaver somniferum*, hirudin from the leech *Hirudo medicinalis*, cephalosporine antibiotics from the fungus *Acremonium chrysogenum*, angiotensin converting enzyme inhibitors of the captopril-type from the lancehead viper *Bothrops jararaca* are just a few examples out of many therapeutic drugs based on chemical scaffolds from natural origin.

It was not a discovery of our present days that natural products represent a valuable source for drug discovery and development [3]. Prior to the advent of modern pharmacology during the past two hundred years, herbal medicine was an indispensable source of treating diseases for mankind from prehistorical ages until today. The World Health Organization (WHO) estimates that more than 20,000 medicinal herbs are still in use nowadays. Even more, more than two thirds of the world's population, especially in developing countries are dependent on traditional medicines, because therapeutics from conventional academic medicine are not affordable for the majority of poor people on this globe [4]. WHO supports member states to develop and implement strategies to strengthen traditional medicine. The development of safe and efficient drugs (either synthetic or natural) at affordable prices should, therefore, be a premier goal for the sake of patients everywhere on this globe [5].

In the past, traditional medicine has been used without the stringent legal regulations of the drug approval processes in industrialized countries nowadays and without the tremendous costs of modern drug development. In contrast to conventional medicine, traditional medicines were largely experience-based. Even in industrialized countries, more than half of all cancer patients use non-conventional forms of medicine, mostly in addition and not as a substitute to standard therapy [6,7]. While traditional medicine has a long-lasting history of application, some other forms of more recent complementary and alternative medicine (CAM) have been neither rigorously investigated with scientific methods nor are records of clinically safe application available. Thus, safety is a critical issue, and any kind of quackery has to be banned.

Safety and toxicity are definitely a critical issue. Among many patients, natural products and phytotherapy are mostly considered as "green and gentle medicine", while many physicians frequently suspect the contrary. Without doubt, any kind of medication – either natural or synthetic – has to be investigated with the same stringent criteria for safety and efficacy. Medicinal herbs and remedies with non-tolerable toxicities have to be identified and eliminated from the market. Those natural products, however, with proven safety and negligible side effects may not only be considered for treatment of diseases, but also for longer-term use to prevent the outbreak of diseases. For instance, classical cytostatic drugs are non-suitable for cancer prevention because of their high toxicities, but some phytotherapies or isolated phytochemicals may be better suited because of their properties to inhibit tumor cell growth concomitantly with low or no side effects.

To find out, which herbal or phytochemical preparations are suited for this purpose, represents a challenge, but this task is also with much attractiveness and excitement. The big question is, whether or not is might be possible to translate experience-based natural products and herbal medicines to evidence-based medicine. A search in the PubMed literature database demonstrated that there is a lot of activities going on, not only to elucidate the cellular and molecular modes of action, but also to evaluate the activity in clinical phase I-III trials.

We screened PubMed with the search tags “cancer and chemoprevention”, “cancer and phytochemical” as well as “cancer and medicinal plant” (Fig. 1). While little publication activity was recorded for the years before 1990, a thriving development took place in the past three decades with increasing annual paper outputs of up to 500 to 700 for each of the three categories in the past three years. This clearly indicates that natural products and medicinal plants gain much attention in the scientific community. There is a considerable interest, whether and how they could be integrated into conventional academic medicine. We have reason to assume that novel strategies based on phytochemicals might be devised to prevent and treat tumors in the years to

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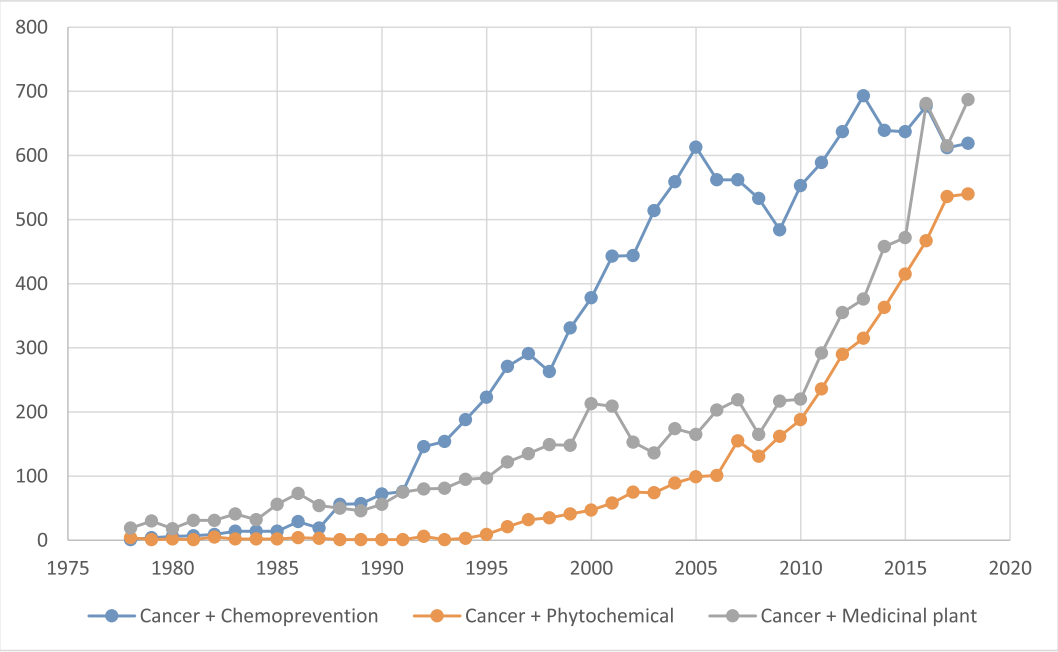

Fig. 1. PubMed-based publication analysis for the time period from 1978 to 2018.

come.

In the present special issue of ***Cancer Letters***, I was fortunate to team up reputed scientists from biomedicine and related fields of research to highlight important aspects of chemoprevention of cancer by natural products (in alphabetical order):

- Nihal **Ahmad** and colleagues: Prostate cancer chemoprevention by natural agents: Clinical evidence and potential implications
- Heike **Allgayer** and colleagues: Prevention of carcinogenesis and metastasis by artemisinin-type drugs
- Atanas G. **Atanasov** and colleagues: Phytochemicals as potent modulators of autophagy for cancer therapy
- Davide **Barreca** and colleagues: Targeting ubiquitin-proteasome pathway by natural, in particular polyphenols, anticancer agents: lessons learned from clinical trials
- Maurizio **Battino** and colleagues: The use of natural compounds for the targeting and chemoprevention of ovarian cancer
- Thomas **Efferth** and colleagues: The naphthoquinone shikonin for cancer prevention and therapy
- Isabel **Ferreira** and colleagues: Antiangiogenic compounds: well-established drugs versus emerging natural molecules
- Carsten **Gründemann** and colleagues: Chemoprevention with isothiocyanates - from bench to bedside
- Eva **Jüngel** and colleagues: Relevance of the natural HDAC inhibitor sulforaphane as a chemopreventive agent in urologic tumors
- Mohammad Amjad **Kamal** and colleagues: Andrographolide, a diterpene lactone from *Andrographis paniculata* and its therapeutic promises in cancer
- Ioannis **Trougakos** and colleagues: Cancer chemoprevention *via* activation of proteostatic modules

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