Editorial

Anticancer Natural Compounds: Molecular Mechanisms and Functions. Part I

In spite of enormous success achieved by the cancer biologists and clinical oncologists alike for the last decades, cancers still presents a great challenge for the researchers and suffering for the patients. While basic mechanisms underlying tumor initiation and progression are unraveling as we speak, as well as novel therapeutic strategies often appear in clinical practice the tumors defend themselves with acquired resistance to therapies using the whole arsenal of their hallmarks. Cancer cells exhibit limitless proliferative potential, sustain self-sufficiency in growth signals, resist anti-growth signals and evade apoptosis induced by the stress signals including therapeutic drugs, stimulate the growth of blood vessels to supply nutrients to tumors, exert their ability for invasion and metastasis, while evading the immune system defense and inducing local chronic inflammation, exhibit deregulated metabolism, and dramatically alter whole genome stability through mutational and epigenetic mechanisms. Natural compounds derived from plants, microorganisms and marine life forms have gained a considerable interest among cancer researchers for the potential to affect multiple cancer hallmarks. Furthermore, many existing anticancer compounds used in clinic today originally derived from the natural habitats. In the present Thematic Issue “Anticancer Natural Compounds. Molecular Mechanisms and Functions”, the investigators from around the world present their views on the role for natural compounds to combat cancer cells *in vitro* and *in vivo*, describing some successful stories leading to the clinical trials, therefore supporting high hopes that natural approaches could be beneficial to combat cancer disease.

The group of Prof. Katrin Sak from Tartu University (Estonia) presents a comprehensive overview of the anticancer activities of flavonoids as plant secondary polyphenol metabolites in the most commonly used human established leukemia cell lines (HL-60, NB4, KG1a, U937, THP-1, K562, Jurkat, CCRF-CEM, MOLT-3, and MOLT-4) is compiled, revealing clear anti-proliferative, pro-apoptotic, cell cycle arresting, and differentiation inducing effects for certain compounds. Considering the low toxicity of these substances in normal blood cells, the presented data show a great potential of flavonoids to be developed into novel anti-leukemia agents applicable also in the malignant cells resistant to the current conventional chemotherapeutic drugs.

The group of Dr. Farooqi working in the Rashid Latif Medical College (Lahore, Pakistan) in collaboration with investigators from National Cancer Research Centre Istituto Tumori “Giovanni Paolo II” (Bari, Italy) presents accumulating evidence that technological advances have started to shed light on underlying mechanisms of resistance against TRAIL-induced apoptosis in cancer cells. The impairment of TRAIL-mediated apoptosis includes various factors ranging from the loss or down regulation of TRAIL receptors or pro-apoptotic proteins to the up regulation of anti-apoptotic proteins. Intriguingly to mention that there is an ever-increasing number of natural herbal extracts (phytometabolites), which have been explored to date for their potential action in restoring apoptosis TRAIL-mediated in cancer cells. In this review, we will highlight the progress in understanding the mechanisms opted by phenolic compounds in overcoming TRAIL resistance.

The groups of Drs. Da-Cheng Hao (Dalian Jiaotong University, Dalian, China) and Pei-Gen Xiao (Institute of Medicinal Plant Development, Beijing, China) provided us the information about new potentials for anticancer activities exhibited by *Ranunculaceae* family, comprising more than 2,200 species in at least 62 genera. They present critical data describing how various medicinal compounds found in *Ranunculaceae* plants, such as alkaloids, terpenoids, saponins, and polysaccharides, have shown anti-cancer activities *in vitro* and *in vivo*. Some *Ranunculaceae* compounds induce the cell cycle arrest and apoptosis of cancer cells or enhance immune activities, while others inhibit the proliferation, invasion, angiogenesis, and metastasis, or reverse the multi-drug resistance of cancer cells thereby regulating all known hallmarks of cancer. These phytometabolites could exert their anti-cancer activities *via* multiple signaling pathways. In addition, absorption, distribution, metabolism, and excretion/toxicity properties and structure/activity relationships of some phytometabolites have been revealed assisting in the early drug discovery and development pipelines. Authors are focusing on the emerging molecular machineries and functions of anti-cancer compounds. Gene expression profiling and relevant omics platforms (*e.g.* genomics, transcriptomics, proteomics, and metabolomics) could reveal differential effects of phytometabolites on the phenotypically heterogeneous cancer cells.

The group of Dr. Patricia Severino (Hospital Israelita Albert Einstein, Sao Paulo, Brazil) has explained for us the importance of compounds derived from the Celastraceae family to combat human cancers, especially squamous cell carcinoma of the head and neck. This review reports studies on chemical constituents isolated from species of the Celastraceae family targeting cancer mechanisms studied to date. These results are then correlated with molecular characteristics of head and neck squamous cell carcinoma in an attempt to identify constituents with potential application in the treatment of this complex disease at the molecular level.

The groups of Profs. Hemanta Kumar Majumder (CSIR-Indian Institute of Chemical Biology, Kolkata, India) and Susanta Roychoudhury (Saroj Gupta Cancer Centre & Research Institute, Kolkata, India) have described the critical role for DNA topoisomerases and their inhibitors derived from natural sources acting as effective anticancer and antibacterial drugs. However, topoisomerase inhibitors have some therapeutic limitations and they exert serious side effects during cancer chemotherapy. Thus, development of novel anticancer topoisomerase inhibitors is necessary for improving cancer chemotherapy. Nature serves as a repertoire of structurally and chemically diverse molecules and in the recent years many DNA topoisomerase inhibitors have been identified from natural sources. The present review article discusses anticancer properties and therapeutic importance of seventeen recently identified topoisomerase inhibitors from natural sources. Structural characteristics of these novel inhibitors provide backbones for designing and developing new anticancer drugs.

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Guest Editor

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