Recent Natural Anticancer Agents

The use of natural products has been the subject of increasing interest in phytochemistry, biochemistry and other fields of research at the chemistry-biology-ecosystems interface. Some natural products are phenolic compounds, flavonoids, alkaloids, terpenes, secondary metabolites of plants that cause several benefits to our health.

In spite of the continued search for new anticancer drugs, cancer remains a leading cause of death. Cancer mortalities are expected to increase to 12.9 million, while cancer incidence itself should rise to 20 million by the year 2030 [1, 2]. Chemotherapeutic strategies are needed that provide selective tumor toxicity. However, the most commonly used cytotoxic (tumor) chemotherapies are largely associated with highly nonspecific cytotoxicity, narrow therapeutic indices, and undesirable side effects. The study of natural products has been the single most successful strategy for the discovery of new medicines used in anticancer therapy. Many studies have ascertained the mode of action and the functional properties of natural anticancer products against the disease, including the carcinogen bioactivation, cell signaling, cell cycle regulation, angiogenesis, oxidative stress and inflammatory response.

Several medicinal chemistry studies report different approaches using these compounds in drug discovery, which comprise synthesis, semi-synthesis, searches for new targets, evaluation of biological activities, and/or theoretical approaches as structure-based approaches, SAR, QSAR, docking and cheminformatics methods [3, 4]. The objective for this thematic issue was to report recent studies on Medicinal Chemistry using Natural Products for the treatment or cure of cancer.

Gastrointestinal stromal tumors (GISTs) are unusual cancers which begin in specialized cells in the gastrointestinal tract wall. Various strategies involving single agents, combinations, and rapid complementary inhibitor cycling are now being used to control such tumors. Based on promising early clinical trial experience, certain novel KIT and PDGFRA tyrosine kinase inhibitors have begun advanced clinical development. Resistance to tyrosine kinase inhibitors has brought immense difficulties, with patients now requiring additional therapeutic options. Our review, Virtual Screening and Molecular Docking: Discovering Novel c-KIT Inhibitors [5], describes and discusses the development in the last five years (2016-2020) of novel c-KIT kinase inhibitors using virtual screening and docking approaches. Computational techniques can be used to complement experimental studies to identify new candidate molecules for therapeutic use. Molecular modeling strategies allow an analysis of the required characteristics that compounds must have to effectively bind c-KIT. Through such analyses, it is possible to both discover and design novel inhibitors against cancer-related proteins that play a critical role in tumor development (including mutant strains). The results presented in the review can be used to develop new compounds/classes of anticancer drugs and help millions of cancer patients.

Cancer is an uncontrolled cell growth that can generate diverse types of cancer, which also present a different behavior in the face of pharmacological treatment. These types are found in one of the three categories, leukemias (also named lymphomas), carcinomas, and sarcomas. In general, cancer's pathogenesis is associated with three genetic mutations, which could emerge from oncogenes, tumor suppressor genes, and/or genes responsible for regulating DNA replication. The term “undruggable” is frequently related to the difficulty in designing drugs for specific targets, such as MYC, MYB, NF-κB, and RAS family of proteins. This last comprises more than 140 proteins, and these are responsible for 30% of mutations in human cancers. Also, there are three ras genes transcribed in human cells, called H-, K-, and N-ras oncogenes. Still, the RAS proteins (farnesyltransferase (FTase) and geranylgeranyltransferase (GGTase) enzymes) perform essential steps in post-translational modification of eukaryotes cells, such as (1) the farnesylation of the cysteine residue at the C-terminal tetrapeptide CAAX; (2) proteolytic cleavage of the three C-terminal AAX oligopeptide; and (3) carboxymethylation of the new C-terminal prenylated cysteine. Thus, the inhibition of this undruggable RAS family of proteins has been considered a promising alternative to design new anticancer agents since they are responsible for many types of human cancers. Then, the manumycin A (obtained from the Streptomyces parvulus Tü64) and its analogs (epoxyquinol core with or without their southern and eastern side chains; and dihydroxydicyclohexenones core) have been described as promising FTase inhibitors, which have demonstrated their benefits against several types of cancer. In the review of the Drs. Silva & Silva-Júnior entitled Inhibiting the “Undruggable” RAS/Farnesyltransferase (FTase) Cancer Target by Manumycin-related Nat-
ural Products [6], a complete introduction regarding cancer and its association with RAS proteins has been provided; also, the prenylation mechanism of the cysteine residue is discussed in detail. Posteriorly, studies involving manumycin-related compounds are described, showing some synthetic routes for obtaining them and utilizing these natural products in monotherapies or combined therapies with other anticancer drugs.

The molecular mechanisms of mitotic cell cycle progression involve very tightly restricted types of machinery, which are highly regulated by a fine balance between the positive and negative accelerators (or regulators). These regulators include several checkpoints that have proteins acting as enzymes and their activating partners. These checkpoints incessantly monitor the external as well as internal environments, such as growth signals, favorable conditions for growth, cell size, DNA integrity of the cell, and hence, function to maintain the highly ordered cell cycle progression by sustaining cell homeostasis and promoting error-free DNA replication and cell cycle division. To progress through the mitotic cell cycle, the cell has to successfully drive past the cell cycle checkpoints. Due to the abnormal behavior of some cell cycle proteins, the cells tend to divide continuously, overcoming the tight regulation of cell cycle checkpoints. Such anomalies may lead to unwanted cell division, and this deregulation of cell cycle events is considered as one of the main reasons behind tumor development, and thus, cancer progression. So, an understanding of the molecular mechanisms in cancer progression might be insightful for designing several cancer treatment strategies. The deregulation in the checkpoints is caused due to the changes brought in the tyrosine residues of TPKs via PDGFR, EGFR, FGFR, and VEGFR-mediated signalling pathways. Therefore, the inhibitors of PDGFR, EGFR, FGFR, and VEGFR-mediated signalling pathways could be potential anticancer agents. The resistance and toxicity in the existing synthetic anticancer chemotherapeutics may decrease the life span of a patient. For a long time, natural products have served as an essential alternative source of therapeutic agents due to resistance and toxicity in the existing synthetic anticancer chemotherapeutics. The study of Dr. Nandi et al. was an attempt to promote the natural anticancer drug development focusing on the updated structural information of PDGFR, EGFR, FGFR, and VEGFR inhibitors isolated from the plant sources. The data used in the study titled Natural sourced inhibitors of EGFR, PDGFR, FGFR and VEGFR-mediated signaling pathways as potential anticancer agents [7] have been collected from internet resources viz. GOOGLE Web, GOOGLE SCHOLAR, and PubMed Central.

We, the Guest-Editors, would like to express our gratitude to the many authors who contributed to this special issue, reporting investigations regarding various aspects of RECENT NATURAL ANTICANCER AGENTS.

REFERENCES


Luciana Scotti  
(Guest Editor)  
Teaching and Research Management - University Hospital  
Federal University of Paraíba  
Campus I, 58051-900  
João Pessoa-PB  
Brazil

Marcus T. Scotti  
(Guest Editor)  
Federal University of Paraíba  
Health Sci. Center, 50670-910  
João Pessoa, PB  
Brazil