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Editorial

Special Issue on "Anticancer Drugs Activity and Underlying Mechanisms"

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1. Introduction

Cancer is a reputed non-communicable disease, namely a non-transmittable illness affecting humankind, which represents a major public health issue and is one of the leading causes of death worldwide [1]. In 2021, it is predicted that there will be 1,898,160 new cancer cases and 608,570 cancer deaths in the United States [2]; in the European Union and in United Kingdom [3], 1,267,000 and 176,400 cancer deaths are predicted to occur, respectively.

Several factors concur with cancer onset and progression, leading to an uncontrollable cell growth, the type of which has been used to classify the different kinds of cancer [1]. To date, surgery, radiation and chemotherapy are considered to be the main approaches to cancer, but an important contribution has been made by an extensive and careful prevention campaign that has been met with public consent. Nevertheless, efforts made by the scientific community, and the continuous increase of improved tools to prevent/treat this disease, numerous obstacles, including the heterogeneity of cancer types/subtypes, the limited treatment efficacy and the occurring toxicity, together with resistance onset and relapse phenomena, make this fight hard to win completely [4]. The chemotherapeutic approach may reach cancer cells in all body tissues and may hamper both the cell growth at the original site and the possible metastases, but the drawbacks represented by dramatic side effects and cancer cell resistance often arise [5]. The ability of cancer cells to exploit the salvage or compensatory pathways that counteract the efficacy of chemotherapy is only the tip of the iceberg. Indeed, a first approach to drug design was based on obtaining a drug targeting a primary (and single) cell component. However, a drug (or its metabolites) can potentially manifest several "off-target" activities, which can be adverse (the so-called negative side effects), neutral, or, hopefully, beneficial [6]. More recently, a multi-target pharmacological drug approach has been recorded, particularly in terms of drug design, discovery, and repositioning [7,8] as well as for the employment of relevant and effective drug combinations/synergy [9]. Great help comes from nature. Indeed, natural compounds and their derivatives represent a valuable source of compounds with anticancer or preventive properties [10].

In this context, great interest in proposing new compounds, or repurposing the old ones, with anticancer properties has been recorded. Thus, this Special Issue, which includes four research papers, a hypothesis, and five literature reviews, offered the opportunity to approach cancer treatment from different points of view.

2. Contributions

The need of suitable therapies to treat cancer is the "primum movens" of the drug discovery process that, as reported by Cava et al. [11], often starts from academic studies that, hopefully, can be translated "from the bench to the bedside" and offer a larger and alternative arsenal to fight cancer. From this point of view, the combined use of in silico and in vivo studies is essential in medicinal chemistry in order to identify putative targets and to explore the anticancer properties of newly synthesized molecules [12] in a given cell model

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prior to proceeding towards in vivo studies. Amongst them, the metal complexes, following the successful employment of *Cis*platin in cancer treatment, has attracted the attention of many researchers because of their different chemical and biological properties [13,14].

In this context, two research studies and one review paper published in this Special Issue are representative of this idea. The first, by Skoupilova et al. [15] reported a series of ferrocene derivatives from the general formula [Fe(η^5-$C_5H_4CH_2$(p-C_6H_4)CH_2(N-het))$_2$], which bear either substituted or unsubstituted saturated five- and six-membered nitrogen-containing heterocycles that are able to inhibit the cervical cancer cell growth, with or without the contemporaneous exposure to ionizing radiation. The authors demonstrated that these complexes possessed higher anticancer activity than *Cis*platin, which was used as reference, and that the exposure to an ionizing radiation increased the anticancer properties, probably because of a radiosensitizing phenomenon that should be further investigated. Cervical cancer cells treated with the lead ferrocene complex underwent intrinsic apoptosis and autophagy with ROS levels increase, as demonstrated by flow cytometry, immunofluorescence, and Western blotting studies. Most importantly, the lead complex exhibited a mild cytotoxic effect on the normal cell lines, which were used as controls, revealing a better cytotoxic profile than *Cis*platin. The second, by Iacopetta et al. [16], describes the study of some N-heterocyclic carbene (NHC)-gold(I) complexes, whose multiple biological activities have already been described [14,17–19], disclosing another important target, namely the intracellular actin, and demonstrating that these complexes hamper actin polymerization by means of docking simulations, immunofluoresce, and direct enzymatic assays. These studies highlight the multi-target potential of NHC-gold(I) complexes, whose anticancer properties come together with negligible cytotoxic effects on the normal cells, paving the way to further modifications with the goal of obtaining new and effective anticancer drugs.

This even more topical field of research has been reviewed by Ielo et al. [20] in detail, who summarized the most salient and up to date papers related to antitumor activity, particularly in terms of breast cancer treatment, drug delivery systems, nanosystems, and complexes based on gold. The authors highlighted how gold-based systems are able to overcome *Cis*platin resistance and its dramatic toxic effects, indicating a desirable therapy personalization that may offer a targeted and more effective treatment and less side effects.

An interesting contribution to the area of drug repurposing against cancer has been made by Barbarossa et al. [21], who reported a library of thalidomide analogs. Thalidomide, a historically well-known drug, has recently been repurposed for its anticancer, antiangiogenic, and immunomodulatory actions, and several analogs with improved efficacy and reduced toxicity have been proposed [22,23]. In this paper, the authors reported the anticancer properties of phthalimide derivatives in a panel of cancer cell lines, mostly against A2058 melanoma cells, individuating a lead compound that is able to block melanoma cell growth by interfering with the tubulin network. Exposure to this compound leads to DNA damage and triggers melanoma cell death by means of the apoptotic mechanism without affecting the growth of normal cell lines.

Again, Catalano et al. [24] reviewed the different properties of diarylureas [8,25], namely ureas bearing two aromatic moieties as substituents, focusing on their role as important pharmacophore in anticancer drugs over the past 10 years. A clinically used member of this class, sorafenib was the lead compound approved from Food and Drug Administration (FDA) and the European Medicinal Agency (EMEA) for the treatment of advanced metastatic hepatocellular carcinoma and advanced renal cell carcinoma, paving the way to other diarylureas derivatives, such as regorafenib, linifanib, tivozanib and ripretinib, which share the ability to inhibit the kinases.

Finally, Iacopetta et al. [26] conducted a literature study reviewing the research conducted on on mono- and bis-Schiff bases within the past few decades, determining several applications and various biological properties [27] and highlighting the compounds with high antitumor properties that fall in the micromolar to nanomolar range. The authors extrapolated upon the literature results, evidencing the versatility of these compounds, both by themselves or in association with metal complexes, indicating a high and broad

range anticancer activity with few or no effects on the viability of normal cells. These compounds are able to target different cell components, such as DNA, kinases, redox enzymes, etc.

Nature is an incredible source of drugs [28–30], including interesting bioactive anticancer molecules, even though they sometimes exhibit bioavailability issues that can be overcome by the use of proper vehicles or chemical modifications [31–33]. Concerning this, Do et al. [34] reported the anticancer properties of 1-(5,7-dimetoxy-2,2dimetyl-2H-cromen-8-yl)-but-2-en-1-on (malloapelta B, malB), isolated from *Mallotus apelta*, which is able to inhibit the activation of nuclear factor kappa B (NF-kB) and is responsible for down-regulating pivotal genes involved in inflammation. However, this compound possesses unfavorable features, such as low solubility and high toxicity; thus, in order to overcome these pharmaceutical limitations, the authors entrapped the malB into nanoliposomes, fully characterized, and studied their anticancer and antitumor properties against the lung carcinoma in vitro and in vivo, demonstrating improved antitumor activity in vivo with respect to the free malB form.

A review study from Chang et al. [35] reported the recent results determining the role of second mitochondria-derived activators of apoptosis (smac) mimetics, birinapant, LCL161, and GDC-0152, in cancer treatment. These molecules, which have entered in phase 1 and 2 clinical trials, are able to induce the non-canonical NF-kB signaling pathway and downregulate the protein expression inhibitor level of apoptosis proteins (IAPs), leading to cells death by apoptosis, even though other mechanisms are still under investigation. The versatility of the smac mimetics resides, for instance, in their possible combination with other clinically used anticancer strategies ("classic" chemotherapy, radiotherapy, and immune therapy) that, together with their safety and the possibility of being coupled with the nanotechnology, make these molecules very attractive in the fight against cancer.

Finally, an interesting hypothesis has been reported by Metzler et al. [36] in their description of a case of a patient with a low-grade ovarian cancer, in which ibrutinib treatment leads to CA-125 suppression, which is reported for the first time in this study. However, further studies are needed in order to understand the underlying mechanisms.

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