Natural Products in Oncology

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In recent decades, increasing interest in the use of natural products in anticancer therapy field has been observed, mainly due to unsolved drug-resistance problems. The antitumoral effect of natural compounds involving different signaling pathways and cellular mechanisms has been largely demonstrated in in vitro and in vivo studies. The encapsulation of natural products into different delivery systems may lead to a significant enhancement of their anticancer efficacy by increasing in vivo stability and bioavailability, reducing side adverse effects and improving target-specific activity. More and more studies in the nanomedicine field aim to design nanostructured systems containing natural compounds for new drug delivery tools in anticancer therapies.

Keywords: natural products ; oncology ; integrative therapies ; nanomedicines ; drug delivery ; synergic effects

1. Limitations of Anticancer Therapies

Cancer is among the leading causes of death worldwide.The number of new cancer cases per year is expected to rise to 23.6 million by 2030. The late diagnosis and non-responsive therapy represent the main causes of higher mortality among many cancer patients.Traditional approaches for cancer treatment include surgery, radio/chemotherapy, immunotherapy, targeted and hormone therapy. Unfortunately, sometimes these approaches are limited because they show low specificity, as they can also affect healthy cells and/or the immune system, then causing negative side effects. In addition, all therapies used in cancer treatment, with the exception of surgery, can induce drug resistance.This phenomenon can be intrinsic or acquired when there is low or no response to anticancer therapy from the beginning or during the course of therapy, respectively. One-drug resistance refers to resistance to one specific drug; when patients show resistance to one drug and become resistant to other unrelated drugs (with different structures and mechanisms of action), the term multidrug resistance (MDR) is employed.A number of factors can contribute to clinical MDR in cancer: factors related to the host (genetic variants, drug-drug interactions, pharmacokinetics) as well as factors strictly associated to tumor mass and its interaction with surrounding tissues [1]. Among tumor factors, alterations in the intracellular drug concentration is one of the most important. Drug-resistant cells accumulate lower drug amount with respect to sensitive cells. This event can be due to a reduced drug diffusion/permeability or to the activity of transmembrane proteins belonging to the ATP-binding cassette (ABC) transporter superfamily. These proteins are often overexpressed and are able to extrude structurally different compounds across plasma and intracellular membranes, through an active mechanism coupled to ATP hydrolysis [2]. In different types of tumors, the induction of drug resistance has been directly linked to the overexpression of ABC proteins as P-glycoprotein (P-gp), multidrug-resistance-associated protein 1 (MRP1) and breast cancer resistance protein (BCRP). The overexpression of P-gp is responsible for the resistance phenotype of a number of neutral and cationic hydrophobic antitumor drugs. Consequently, in order to overcome this form of MDR, in recent years, many studies have been aimed at finding substances, including natural ones, able to inhibit ABC transporter activity increasing intracellular drug concentration [3]. Despite the positive outcomes in the field of cancer research, considering all factors responsible for limited chemotherapy success, a lot of studies are continuously concerned to develop more efficient therapeutic strategies, in order to selectively target cancer cells, avoid a MDR response, overcome biological barriers and achieve a spatial, temporal and dose control of drug release [4]. Natural products, either in their naturally occurring forms or in their synthetically modified forms, are an important source for cancer preventive and chemotherapeutic agents. Indeed, considering the period between the 1940s and the end of 2014, natural products or compounds derived from them represent almost 50% of all small molecules approved for cancer therapy [5]. Unfortunately, the use of most natural products in anticancer therapy, as well as against infections or other diseases, is limited due to their low bioavailability, directly related to both their lipophilic and hydrophilic nature, and to the possible induction of cytotoxic effects. Nanomedicine-based strategies allow to improve the bioavailability of many natural compounds as well as to increase their selective activity against cancer cells [6].

2. Natural Products in Oncology

Natural products represent a large family of different chemical entities with a wide variety of activities and pharmacological effects. They originate from bacterial, fungal, plant and marine animal sources and have several applications in different sectors such as food, agricultural, pharmaceutical, packaging and cosmetics. They are often used as flavorings, beverages, repellents and fragrances as well as for their medicinal purposes [7]. In recent years, biomedical research has focused its attention at searching substances of natural origin as possible chemosensitizing and chemopreventive agents [8]. Indeed, most of the anticancer drugs employed in therapy derive from natural substances or are related to them. In addition, the molecular diversity of these products with great biological potential have yet to be studied and discovered [9]. In 1940, the first antitumor antibiotic, actinomycin D, was isolated from the fungus Actinomyces antibioticus [10]. Since then, many substances of natural origin have been subjected to in vitro and in vivo studies to assess their ability to improve the therapeutic index of chemotherapy. Among them, Taxanes are derived from plants belonging to the genus Taxus. Paclitaxel (PTX or Taxol®), collected from the bark of *Taxus brevifolia*, is a semi-synthetic form of taxane and acts as a microtubule-stabilizing drug inducing mitotic arrest and cell death [11]. Nowadays, the drug represents a first-line treatment for ovarian, breast, lung and colon cancer and a second-line treatment for AIDS-related Kaposi's sarcoma. There are many *in vitro* and in vivo studies focusing on drug delivery systems of natural compounds in the field of oncology aimed at improve their solubility, bioavailability and selectivity [12][13]. Liposomes represent one of the most employed nanoparticle systems for cancer therapy. They are able to encapsulate both lipophilic and hydrophilic compounds within their phospholipid bilayer and the inner core. Many studies have shown that encapsulating natural substances in liposomes can improve their biological activity compared to non-encapsulation [14]. One example is represented by doxorubicin: similar to other anthracycline compounds, the free drug induces severe cardiotoxicity in many patients, and its encapsulation is able to decrease free doxorubicin toxicity. Several *in vitro* and preclinical studies have employed doxorubicin encapsulated inside micelles, metallic nanoparticles, nanodiamonds. These formulations also demonstrated a slower drug plasma clearance, enhanced circulation and half-life [15]. To date, many nanodelivery systems have been developed and reported to effectively bypass MDR both in vitro and in vivo. The encapsulation of chemotherapeutics can avoid their direct interaction with ABC transporters at both plasma and intracellular membranes, thus modifying the intracellular drug concentration and localization, and inducing apoptotic cell death [16]. Nano-based systems are also useful to deliver multiple natural compounds in order to overcome MDR-associated side effects. In a recent in vitro and in vivo study, resveratrol and doxorubicin were co-encapsulated in poly(lactic-co-glycolic acid) (PLGA)-based nanoparticles. Resveratrol is a natural stilbene and a non-flavonoid polyphenol, present in grapes, peanuts and red wine. This phytoestrogen possesses anti-oxidant, anti-inflammatory, cardioprotective and anti-cancer properties [17]. The PLGA-based nanoparticle system was able to deliver both compounds into the nucleus of doxorubicin-resistant human breast cancer cells, thus increasing cell cytotoxicity. Nanoparticles employed overcame doxorubicin resistance by inhibiting the expression of P-gp, MRP-1 and BCRP drug transporters, and inducing apoptosis through NF-κB and Bcl-2 downregulation. In addition, this delivery system was also effective in inhibiting *in vivo* tumor growth with no significant induction of systemic toxicity [18]. The plant alkaloid voacamine, isolated from the bark of the *Pescheria fuchsiaefolia* tree, is able to enhance doxorubicin cytotoxicity and induce chemosensitizing effect on cultured multidrug-resistant U-2 OS-DX osteosarcoma and melanoma cell line Me30966 when used at noncytotoxic concentrations [19]. Voacamine encapsulated into different cationic liposome formulations was more efficient than free molecule to revert resistance of osteosarcoma cells resistant to doxorubicin. Curcumin is a natural polyphenolic compound extracted from the plant turmeric; a lot of in vitro and some in vivo studies demonstrated its anticancer properties in breast, prostate, bone, cervices, lung and liver cancer cell lines [20]. Unfortunately, free curcumin is not soluble in water and not very bioavailable, features that limit its application in the clinics; the encapsulation in nanoparticles such as liposomes has solved these problems [21]. Liposomal curcumin (Lipocurc™) can reduce pancreatic and colorectal cancer growth. In a phase I dose escalation study the safety, pharmacokinetics, tolerability and activity of intravenously administered liposomal curcumin were evaluated in patients with locally advanced or metastatic cancer [22]. Artemisinin, discovered by Youyou Tu in 1972, is used as an antimalarial for the treatment of multi-drug resistant strains of Plasmodium falciparum that causes malaria infection. Artemisinin is a sesquiterpene lactone obtained from sweet wormwood, Artemisia annua. This substance and its derivatives (artemisinins) show good antitumoral activity [23]. Artemisinin is loaded in many nanocarriers such as liposomes, niosomes, micelles, solid lipid nanocarriers, nanostructured lipid carriers, nanoparticles, fullerenes and nanotubes with different therapeutic applications. Nowadays, there are many studies on Artemisinin and its encapsulation inside nanoparticles to improve drug delivery and to increase blood circulation, as the therapeutic value of Artemisinin is limited due to a low bioavailability and a short half-life [24]. Many *in vitro* studies on resveratrol have reported its involvement in different cellular responses, such as cell cycle arrest, induction of differentiation, apoptosis and growth inhibition in several types of cancer, principally prostate and colon cancers [17]. Unfortunately, resveratrol displays low bioavailability, low water solubility and instability. Its incorporation inside nanoparticles improves the effects against cancer cells [25][26]. Other natural substances with promising anticancer properties are essential oils (EOs). They are a complex mixture of hydrophobic and volatile

compounds synthesized from aromatic plants. They are constituted of terpenoids, phenol-derived aromatic components and aliphatic components. EOs have been widely used for their antimicrobial, antioxidant, anti-inflammatory, immunomodulatory and anticancer properties in vitro. The characterization of EOs is made difficult by their complexity and by the different compositions present in the same oil having different geographical origins. Encapsulation of EOs in micro or nanometric systems is an interesting strategy to provide better stability to the volatile compounds and protect them against environmental factors that may cause chemical degradation. In addition, it can increase EOs bioactivity, decreasing their volatility [27]. In the essential oil of oregano, the monoterpene Carvacrol is present. It has been studied for its therapeutic properties. It has been studied for its therapeutic properties, especially in the control of painful conditions and inflammation during cancer condition. The encapsulation of carvacrol in a complex of β-cyclodextrin and its oral administration in mice with sarcoma reduced hyperalgesia. However, pure carvacrol did not cause significant changes in nociceptive responses. These results produced evidence that the encapsulation of carvacrol in β-cyclodextrin can be useful for the development of new options for pain management [28]. Another constituent of natural products studied is *Aloe emodin* (1,8-dihydro-3-hydroxymethyl-anthraquinone, AE) a hydroxyanthraquinone present in Aloe vera leaves. It shows multiple properties (antifungal, antibacterial, antiviral activities, liver protective). A lot of *in vitro* studies have demonstrated the ability of AE to reduce the viability and proliferation of different cancer cell lines, induce the apoptotic cell death, inhibit adhesion and migration process [29]. Unfortunately, AE application in anticancer therapies might be hindered by its scarce solubility in aqueous environment. Several studies are currently searching for AE loading into nanocarriers, to obtain a selective delivery to target sites. A recent study showed that cationic liposomes (gemini-based) are able to efficiently load AE (which possesses a weak acid nature) in their internal aqueous phase, in response to a pH difference between the inside and outside of the liposomes [30].

3. Conclusions

Traditional approaches for cancer treatment are sometimes limited because of their low specificity, responsible for severe side effects and toxicity, and the possible induction of the MDR phenotype. As a consequence, the searching for more effective anticancer therapeutic strategies is increasingly driven by the need to selectively kill cancer cells, defeat the MDR phenomenon and increase the specificity of a drug through the spatial, temporal and dose control of its release. Natural products represent an important source for the discovery of novel anticancer drugs to be used both at preventive and therapeutic level. Unfortunately, some of the natural compounds' features restrict their application in anticancer therapy. Strategies based on nanomedicine and nanodelivery systems improve the efficacy of natural compounds with anticancer properties, increasing their solubility, bioavailability, selectivity and reducing their systemic toxicity. Multifunctional nanocarriers have been recently designed to gradually and selectively release combined compounds (currently used antineoplastic drugs plus natural products) at specific tumor sites. This combination strategy is proving more and more effective for both anticancer therapeutic and chemosensitizing purposes.

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