



Natural Products as Treatment against Cancer: A Historical and Current Vision

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Abstract

Based on the potential of natural products for the discovery of new compounds for the treatment of diseases, the purpose of the present review was to investigate the importance of natural products for the development of treatments for cancer. Since the 1980s, a total of 174 new compounds with indications for cancer treatment have been approved for commercialization, of which a total of 93 (53%) were natural products or derived directly or based on them. Due to the relative ease of access to the plants, most of the discoveries of anticancer compounds were derived from plants, among these discoveries the drug obtained from the bark of *Taxus brevifolia* (paclitaxel) presents one of the most successful stories in plant-based research. However, marine and microbiological organisms have also provided many promising bioactive compounds with high therapeutic potential such as trabectedin, cytotoxic antibiotics of the Anthracycline class and enediyines. In conclusion, the natural products were essential importance for the discoveries of treatments for the cancer, with prospect of more discoveries and innovations with the advent of new technologies.

Keywords: Natural products; Cancer; Treatments

Introduction

Historically, natural products from plants and animals have been the source of virtually all medicinal preparations and, more recently, natural products continue to provide prototypes for pharmacologically active compounds, particularly as anticancer and antimicrobial agents [1].

The study by [2] emphasizes the importance of research on natural products, since between the beginning of 1981 and the end of 2014, a total of 136 drugs against cancer were recorded in the world, with only 17% totally synthetic origin and 83% of these drugs were natural products or were based on them, or imitate natural products. One finding that amplifies the relevance of research with natural products is that one of the most famous antineoplastic drugs, paclitaxel, used for the treatment of breast cancer, was isolated from the bark of the *Taxus Brevifolia* [3].

Despite the success of these natural products, most plant species have not been systematically investigated in drug discovery campaigns. Even traditional plant-based medicines that are used by different crops still need to be further explored [1]. In this context, Brazil has the greatest diversity of plant species in the world; on the other hand, less than 10% were evaluated for their biological characteristics and less than 5% were submitted to detailed phyto chemical studies. Within this universe, they are sparsely studied as regards biological activities and especially in relation to cytotoxicity in tumor cell lines [4].

Based on the success and potential of natural products for the discovery of new compounds for the treatment of diseases, the purpose of this review was to investigate the importance of natural products for the development of cancer treatments.

Methods

The research was carried out in 2 databases of scientific literature: PubMed and Scientific Electronic Library Online (SciELO), using as keywords the terms "Natural products and Cancer". The research was carried out until January 2018.

Natural products

Natural products and their derivative compounds are the most successful source in the discovery of potential drugs. Medicinal plants have evolved and adapted over millions of years to resist

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Received Date: 11 Dec 2018

Accepted Date: 02 Jan 2019

Published Date: 09 Jan 2019

Citation:

Amaral RG, dos Santos SA, Andrade LN, Severino P, Carvalho AA. Natural Products as Treatment against Cancer: A Historical and Current Vision. Clin Oncol. 2019; 4: 1562.

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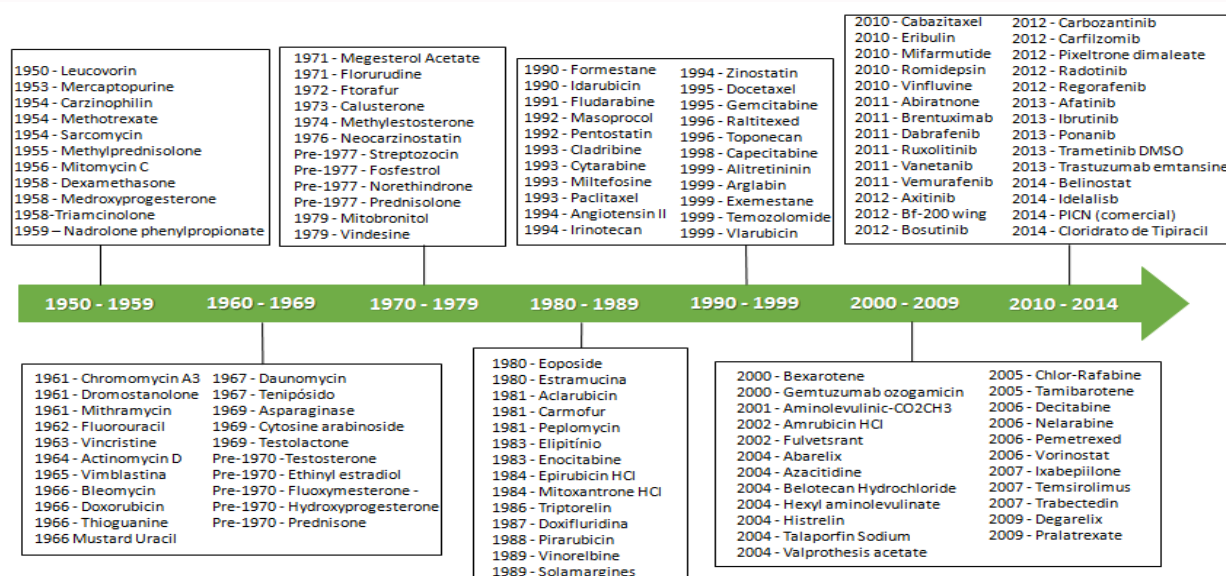


Figure 1: Anticancer drugs approved for marketing between 1950 and 2014, originating directly from or based on natural products or that imitate natural products.

bacteria, insects, fungi and climates to produce structurally diverse unique secondary metabolites. Its ethno pharmacological properties were used as primary source of drugs for the discovery of drugs [3].

According to the World Health Organization (WHO), 80% of people still rely on traditional plant-based medicines for primary health care and 80% of 122 plant-derived drugs were related to their original ethno pharmacological goal. Knowledge associated with traditional medicine promoted new investigations of medicinal plants as potential medicines and led to the isolation of many natural products that became well known pharmaceuticals [3].

Antibiotics (e.g., penicillin, tetracycline, erythromycin), antiparasitics (e.g. avermectin), antimalarials (e.g., quinine, artemisinin), lipid control agents (e.g. lovastatin and analogs), immuno suppressants for organ transplants for example, cyclosporin, rapamycins) and anticancer drugs (eg, paclitaxel, doxorubicin) have revolutionized medicine [5].

The Dictionary of Natural Products recorded approximately 200,000 secondary plant metabolites to date, including about 170,000 unique structures. Approximately 15% of drug interventions in the ClinicalTrials.gov database are plant-related, with about 60% of these drug sources grouped into only 10 taxonomic families [4]. Although natural products have been widely used in historical drug discovery efforts, there are still many resources that could be exploited in modern research on natural products.

It should be remembered that nature took three billion years to refine its chemistry and that less than 10% of the world's biodiversity was assessed for potential biological activity. So by observing temporal and evolutionary characteristics, we are only beginning to explore the molecular diversity of natural products, and many compounds with great biological potential are waiting to be discovered, guarding the challenge of how to access this natural chemical diversity [3,6].

Natural products have been a rich source of compounds for drug discovery. However, its use has declined over the past two decades, in part due to technical barriers to tracking natural products in high-throughput assays against molecular targets. Currently, there

is substantial decline in new drug approvals and imminent loss of patent protection for major drugs [5,7].

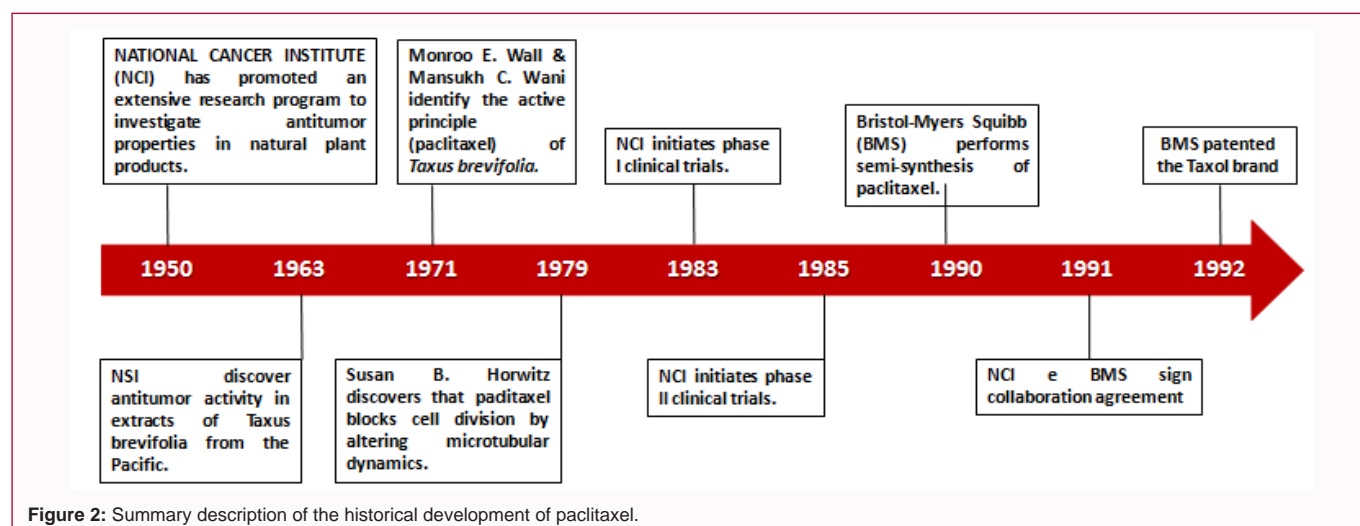
However, untapped biological resources, "smart screening" methods, robotic separation with structural analysis, metabolic engineering and synthetic biology offer innovative technologies for the discovery of new natural medicines. Advances in rapid genetic sequencing, coupled with the manipulation of biosynthetic pathways, can provide a vast resource for the future discovery of pharmaceutical agents [5,7].

Natural products in cancer treatment

With cancer now one of the most deadly diseases in the world, with growing prospects for the coming decades (due to population aging), there is considerable scientific and commercial interest in the discovery of new anticancer agents from sources of natural products [4,8]. So efforts are being made by researchers in an attempt to explore nature in search of new substances with potential anticancer activity or that improve the action of existing compounds [9].

Drug discovery programs with cancer activity began with four programs related to World War II and the effects of drugs discovered, provided the impetus to establish in 1955 the national drug development effort known as the National Service Center for Chemotherapy against the Cancer. The ability of combined chemotherapy to cure acute childhood leukemia and advanced Hodgkin's disease in the 1960s and early 1970s overcame the prevailing pessimism about the ability of natural drugs to treat advanced cancers, facilitated the study of adjuvant chemotherapy, and helped to promote the national cancer program [10].

The potential for the use of natural products as anticancer agents was recognized in the 1950s by the National Cancer Institute (NCI) and since then, several studies have provided valuable insights into the discovery of naturally occurring new anticancer agents. In the 1980s, the development of new screening technologies led the research of new anticancer agents in plants and other organisms, focusing on the tropical and subtropical regions of the world [4]. In (Figure 1), all drugs approved for commercialization from 1950,



whether originating from natural products per se or based on it, or which mimic natural products in one form or another, are described.

In the period between 01/01/1981 and 12/31/2014 (34 years) a total of 174 new compounds with indication for the treatment of cancer were approved for commercialization. Of these, 56 (32%) were natural unmodified products or direct derivatives, 37 (21%) inspired by chemical structures of natural products, 43 (25%) were synthetic chemical entities, 33 (19%) of non-biological origin and 5 (3%), vaccines. Thus, a total of 93 (53%) are natural products, derived directly or based on them [2].

Among the currently used drugs for cancer treatment, paclitaxel (Taxol) presents one of the most successful histories in the research of natural products. In 1962, the United States Department of Agriculture (USDA) first collected the bark of *Taxus brevifolia* as part of its exploratory plant screening program at the National Cancer Institute (NCI). In 1963, the NCI discovered the antitumor activity of extracts of the bark of *Taxus brevifolia* and in 1971 its active principle, paclitaxel, was identified. However, the major problem for drug production is that about three mature trees of 100 years are needed to provide 1 gram of the active ingredient, since a course of treatment may need 2 grams of the drug. However, in 1990 the pharmaceutical industry achieves the semi synthesis of paclitaxel and in 1993 the product is available for those afflicted with the disease. Today, it is one of the most used drugs for breast cancer, with a demand of about 100 kg to 200 kg per year, that is, 50,000 treatments per year [3]. In (Figure 2) the description of the historical development of paclitaxel is illustrated.

With technological development and advancement in the biological and molecular understanding of cancer, methods of screening for naturally occurring compounds have gained specific target approaches. Several of these models have been developed and tested against natural compounds. As the interaction between p53 tumor suppressor protein and its regulatory protein MDM2 it served both as a model for protein-protein interactions and as a challenge to find potent and selective inhibitors. The screening of a large collection of microbial extracts led to the identification of chlorofusin, chalcona and nutlin3 as inhibitors of the p53-MDM2 interaction [11,12].

Members of the B-cell lymphoma (BCL-2) family of proteins regulate apoptosis. Anti-apoptotic members (such as BCL-XL), which are usually over expressed in cancer cells, dimerize with pro-

apoptotic members (such as BAD or BAX). Two natural products, gossypol and purpurogalline have been found to inhibit binding of BCL-XL to the α -helical domain of pro-apoptotic proteins. Thus, the experimental study with gossypol paved the way for synthetic inhibitors of BCL-2 that is now in clinical trials [7].

Natural products were also used to disrupt interactions between proteins and RNA. For example, spliceostatin A, a synthetic derivative of a natural product from a broth of a *Pseudomonas* species, blocks the union and nuclear retention of pre-mRNA, probably by binding to the small ribonucleo protein SF3b complex and blocking its Association. The spliceostatin analogue FR901464 destroys tumor cells in vitro and prolongs survival in cancer cancer models, and simpler spliceostatin analogues (such as sudemicins) are also being studied as possible anticancer derivations. Didehydro-cortistatin A (a synthetic variant of the steroidal alkaloid corticostatin). In general, protein-protein interactions are being recognized as potential targets for natural compounds and it is likely that more targets will emerge for future developments [13].

Natural products of microbiological origin

Antitumor antibiotics are one of the classes of cytotoxic agents that also had their studies stimulated in programs during World War II and that currently have significant importance in the fight against cancer [10]. In 1941, one of the first candidates for antineoplastic antibiotics, actinomycin, was isolated from the culture of *Streptomyces antibioticus*; however, due to its lack of specificity and violent toxic effects, its use in humans had many limitations. Later, it was possible to isolate actinomycin C from cultures of *Streptomyces chrysomallus*, followed by actomycin D with more significant activities in neoplasms although its use would continue to be limited due to the severe toxicity [14].

These early antitumor antibiotics established initial interest in the search for more active compounds, and this effort resulted in a number of active chemotherapeutic agents such as mitomycin C and bleomycin, as well as the emergence of important classes of antitumor antibiotics, anthracyclines and enedynes [14]. Among these classes, the most relevant are anthracyclines, which were isolated from *Streptomyces peucetius* in the early 1960s and referred to as doxorubicin and daunorubicin. Only two more anthracyclines reached clinical approval; idarubicin and valrubicin [17]. Antitumor antibiotics of the anthrax cycline class interfere with the action of

the topoisomerases, enzymes involved in DNA replication. These molecules are capable of exerting their action independently of the cell cycle phase, although they are more efficient in mitotic process cells [15].

Doxorubicin is one of the most potent antineoplastic drugs prescribed alone or in combination with other agents, the class of compounds having the broadest spectrum of activity. Many studies have attributed the antitumor activity of doxorubicin specifically to its ability to interleave in the DNA helix and/or to covalently bind the proteins involved in DNA replication and transcription. Such interactions result in DNA breakdown, inhibition of RNA replication and transcription and consequently protein synthesis, leading to cell death [16].

During the 1980s, a new class of natural products called enediynes was introduced with the structural elucidation of neocarzinostatin and calicheamicin [17]. These new antibiotics share potent antibiotic and antitumor activity. Many efforts have been made to develop new enediynes as anticancer agents. Since then several other agents have appeared as esperamicin, dinemicina, kedarcidina, namenamycin, C-1027 chromophore, maturepeptina, N1999A2 and shishijimicina, and recently found unciamycin [18-25].

Natural products of marine origin

Until then, relative ease of access to the plants, it turned out that most of the discoveries of anticancer compounds were derived from plants. However, marine organisms also provided many promising bioactive compounds with high therapeutic potential, but their development was severely reduced because of difficulties in obtaining adequate amounts of such compounds. For example, the anticancer agent ecteinascidin-743 (known as trabectedin) was the first to be isolated from *Ecteinascidia turbinata* in 1984. However, yields were extremely low: one ton of animals were required to isolate one gram of trabectedin. This was solved after 15 years by the semi-synthetic process initiated with safracin B, which is obtained by fermentation of the bacterium *Pseudomonas fluorescens* [1].

Recent works suggest that marine organisms, and perhaps a group of organisms, fungi of marine origin, will play an increasingly important role in the future, especially due to the impressive advances in organic synthesis to solve the supply problems inherent to this material source. In the future, with the advent of genetic techniques that allow isolation and biosynthesis, microbes and their marine invertebrate hosts may be the new frontier for the discovery of natural products, although plants may also offer a wealth of new resources [6].

Natural products and the resistance of canceriginal cells

As a recent ascent, natural products have been treated as a possible alternative to solving a recurring cancer problem, multidrug resistance. Chemotherapy is the standard internal medical treatment for cancer. However, cancer cell resistance to almost all types of chemotherapy drugs and targeted medications has become prevalent and approximately 80% to 90% of deaths in cancer patients are directly or indirectly attributed to drug resistance.

Although a large number of genes, proteins and molecular pathways have been identified and described, complex molecular networks hinder strategies for overcoming resistance through a single target. So natural products, which are also known as "dirty" compounds with multiple potential targets, can help correct and maintain the

robustness of signaling networks. Therefore, natural products can be used to prevent or treat drug resistance in cancer chemotherapy by applying two strategies: increasing intracellular concentrations of chemotherapeutic drugs and/or inducing alternative processes to cell death by apoptosis [19,26-35].

Conclusion

In conclusion, the present review demonstrates that natural products derived from medicinal plants of marine and microbial origin have an important contribution to the discovery and development of new substances with therapeutic potential against cancer and as a possible alternative to resistance demonstrated by cancer cells at multidrug. However, it is evident that in the face of the world's natural diversity, there is still much to be explored and with the advent of technology, screening programs tend to provide several new prototypes that are candidates for pharmacologically active compounds, which will increase the speed of exploitation of the elements of nature.

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