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Review

Molecular approaches towards development of purified natural products and their structurally known derivatives as efficient anti-cancer drugs: Current trends

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ABSTRACT

Several natural products and their derivatives, either in purified or structurally identified form, exhibit immense pharmacological and biological properties, some of them showing considerable anticancer potential. Although the molecular mechanisms of action of some of these products are yet to be elucidated, extensive research in this area continues to generate new data that are clinically exploitable. Recent advancement in molecular biology, high throughput screening, biomarker identifications, target selection and genomic approaches have enabled us to understand salient interactions of natural products and their derivatives with cancer cells vis-à-vis normal cells. In this review we highlight the recent approaches and application of innovative technologies made to improve quality as well as efficiency of structurally identified natural products and their derivatives, particularly in small molecular forms capable of being used in "targeted therapies" in oncology. These products preferentially involve multiple mechanistic pathways and overcome chemo-resistance in tumor types with cumulative action. We also mention briefly a few physico-chemical features that compare natural products with drugs in recent natural product discovery approaches. We further report here a few purified natural products as examples that provide molecular interventions in cancer therapeutics to give the reader a glimpse of the current trends of approach for discovering useful anticancer drugs.

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1. Introduction

Compounds with biological activities, and products derived from natural sources, e.g. plants, animals and microorganisms are defined broadly as "natural products" that constitute the major sources of chemical diversity, in purified or structurally identified form. These compounds can also be classified as crude therapeutic formulations, semi-synthetic natural products, natural product derived compounds, herbal medicines and complementary and alternative medicines. Many drugs used recently for therapeutic applications are complex natural products or natural product derivatives (Salvador et al., 2012; Clardy and Walsh, 2004). Cancer remains a major public health issue as more than one million people are diagnosed with cancer each year (Howlader et al., 2012). Development of resistance against chemotherapy, toxicity and side-effects necessitates the search for relatively non-toxic drugs or natural products, to wage a more humane war against cancer (Pan and Ho, 2008). However, orthodox approaches for cancer therapy including surgery, radiotherapy and adjuvant therapies are still necessary.

In this review, we will focus more on the following aspects: (a) evaluation of purified natural products and their further strategic up-gradation for more specific use in future anticancer drugs; (b) developmental application of innovative technologies useful in tissue-specific targeting, chemo-resistant cancer types and (c) recent trends of molecular approaches towards targeted cancer therapeutics.

But at the onset, we will briefly dwell upon the features that compare natural products with drugs. The architectural determinants that highlight comparison between natural products and synthetic drug molecules in pharmacological applications have been depicted in Fig. 1 and outlined below.

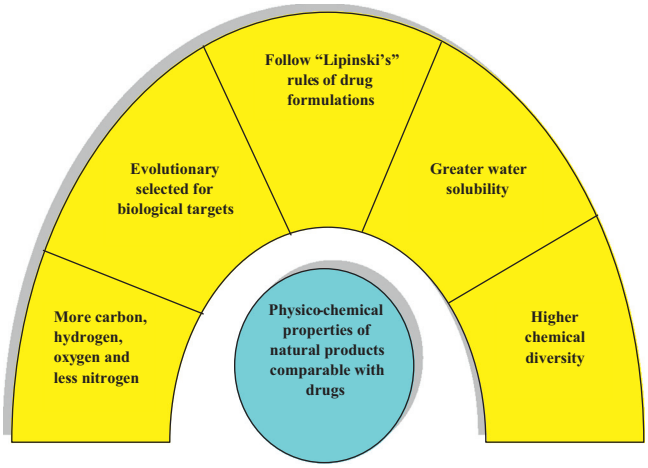

Fig. 1. Physico-chemical properties of natural products comparable with drugs—indicate natural products contain more carbon, hydrogen oxygen and less nitrogen; evolutionary selected as biological targets; greater water soluble in nature and contain huge chemical diversity. These are important features to follow pharmacokinetics guidelines of "Lipinski's rule" of drug formulation and adsorption in body.

Both the natural products and synthetic molecules share high chemical diversity, biochemical specificity, molecular mass, number of chiral centres, molecular flexibility and distribution of heavy metals suitable for therapeutic applications (Henkel et al., 1999). Compared to synthetic medicinal agents, natural products contain more number of carbon, hydrogen, oxygen and less nitrogen and other elements. Further, the molecular rigidity is greater in natural products as compared to synthetic drugs and other combinatorial drugs (Feher and Schmidt, 2003). Many useful natural products have high polarity rendering them greater water solubility, an important feature in maintaining pharmacokinetics guidelines of oral administration in terms of better adsorption, distribution, metabolism and elimination from body (Butler, 2008). Natural product structures are evolutionarily selected to interact with a wide variety of proteins and other biological targets for specific purposes. The ability of natural products to bind a variety of protein domains and folding motifs leads to modulate or inhibit protein–protein interaction, making these molecules behave as effective modulators of cellular processes such as immune responses, signal transduction, mitosis and apoptosis. By virtue of increased size and binding affinity to gene products natural products provide effective scaffolds for the biological function (Peczuh and Hamilton, 2000). Most of the natural products show several key properties as specified in the "Lipinski's rule of five" (Lipinski et al., 1997) appropriate for oral administration. Thus, these criteria clearly point out that natural products can play a significant role in the selection and design of the most effective drug in respect of its specific application.

2. Recent approaches towards molecular cancer therapies with purified natural products

Cancer is a disease of uncontrolled proliferation and growth of cells at inappropriate times and locations in the body. When cells acquire mutations that affect the regulation of cell division, they undergo unlimited multiplications to form tumors (Hanahan and Weinberg, 2011); these proliferating cells consequently transform into malignant ones and invade other tissues as a result of metastasis.

Recent drug discovery program seeks for rapid screening, hit identification and hit-to-lead generation. In these circumstances, traditional natural product development programs which are based on extract-library screening, bioassay-guided isolation, structure elucidation and subsequent product scale up processes, are lagging behind as compared to the approaches that have largely been utilized in the synthetic chemical process. However, the high throughput screening methods in combination with approaches of human genetics and genomics towards functional validation of target regions, especially by over expression or knockdown by RNA-interference in transgenic animals and model organisms (Benson et al., 2006) are yielding interesting results. This outcome is also creating interest in pursuing studies on natural products as a source of chemical diversity and lead generation. New approaches with natural products for drug