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Research review paper

Molecular biodiversity and recent analytical developments: A marriage of convenience

Strahil Berkov [a,b,*], Blaga Mutafova [c], Philippe Christen [d]

[a] Institute of Biodiversity and Ecosystem Research, Bulgarian Academy of Sciences, 23 Acad. G. Bonchev str., Sofia 1113, Bulgaria
[b] AgroBioInstitute, Agricultural Academy, 8 Dragan Tsankov str., Sofia 1164, Bulgaria
[c] The Stephan Angeloff Institute of Microbiology, Bulgarian Academy of Sciences, 26 G. Bonchev str., Sofia 1113, Bulgaria
[d] School of Pharmaceutical Sciences, University of Geneva–University of Lausanne, Quai Ernest-Ansermet 30, CH-1211 Genève 4, Switzerland

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ABSTRACT

Nature has developed an outstanding bio- and molecular diversity as a result of billion years of evolution resulting in a tremendous number of secondary metabolites. Among them a small part has been so far explored for discovery of lead compounds. The lead discovery from natural sources is a technological challenge for the pharmaceutical industry. The bio- and molecular diversity in plants, animals and microorganisms, as sources for new leads, and the remarkable recent developments in NMR, mass spectrometry coupled with advanced separation techniques (LC and GC), high throughput screening, and structure-based virtual screening are discussed in this article.

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Introduction

The Ebers Papyrus, dated back to 2900 BC, is one of the earliest records on natural products describing utilization of plants as remedies. Later, many prescriptions and plant-based drugs have been documented in the Chinese Materia Medica (1100 BC). Theophrastus (~300 BC), considered as the father of botany and the Greek physician Dioscorides (100 AD), among many others reported on the properties of plants as medicines (Dias et al., 2012). Eighty percent of all medicines were obtained from plants till the early 1900s (McChesney et al., 2007). In the 20th century, natural products have continued to be an important source of leads, however, many synthetic and semi-synthetic drugs have been introduced on the pharmaceutical market. Medicines containing natural compounds such as morphine, atropine, cocaine,

* Corresponding author at: Institute of Biodiversity and Ecosystem Research, 23 Acad. G. Bonchev str., Sofia 1113, Bulgaria. Tel.: +359 897063311.
E-mail address: berkov_str@yahoo.com (S. Berkov).

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quinine, and digoxine have been used for centuries. Natural products, such as the anti-malarial drug artemisinin, the anti-cancer agents taxol, and camptothecin, and the anti-Alzheimer's alkaloid galanthamine have been well-established on the market during the last decades (Harvey, 2000). Thirty-six new drugs originating from plants, fungi, bacteria and animals have been approved by the FDA from 2000 to 2010 (Lam, 2007; Mishra and Tiwari, 2011). Fig. 1 presents structures of some natural product based drugs which are marketed or are under clinical trials.

Over the past 25 years, two-thirds of the developed drugs for the treatment of human diseases have been derived from natural products or their derivatives (Newman and Cragg, 2007). Although natural products offer a greater structural diversity than standard combinatorial chemistry (Harvey, 2000), their use in drug discovery programs has been decreased by the pharmaceutical companies due to difficulties in supplying samples from different habitats, small amounts of bioactive compounds in complex mixtures, slowness of isolation and structure determination process, high cost, and complex structures which are difficult to modify in lead optimization stage (Bindseil et al., 2001; Harvey, 2008; Lam, 2007).

In the recent years, natural product research has been experiencing a renaissance due to the technological advances allowing more efficiently the investigation of the inexhaustible diversity of natural compounds. Our vision of biodiversity and possibilities to search for new bioactive molecules is changing with the progress of molecular biology and technologies. The aim of this article is to outline the dimensions of natural molecular biodiversity, as well as to review the recent advance in the technological platforms for discovery of new lead molecules from Nature.

Biodiversity and molecular biodiversity

Nature has developed an enormous biodiversity during several billion years of evolution. It involves diversity of genes, species and habitats which reflects different aspects of the life history. The diversity of alleles, genes, and organisms, and processes which increase this diversity, such as mutation and gene transfer, drive the evolution and speciation. A recent study predicts that there are about 8.7 million eukaryotic species, of which ~2.2 million marine organisms, meaning that some 86% of existing species on Earth and 91% of species in the oceans have not been yet described (Mora et al., 2011). The highest biodiversity, both, terrestrial and marine tends to be near the Equator where the average temperatures and primary production (the rate of energy capture and carbon fixation by primary producers) are higher than other parts of the Earth (Gaston and Kevin, 2000). Living forms, called extremophiles, can be found in niches that are extraordinarily hot, cold or acidic like the hydrothermal systems where the temperatures are above 85 °C (Pituka and Hoover, 2007). Unique habitats with

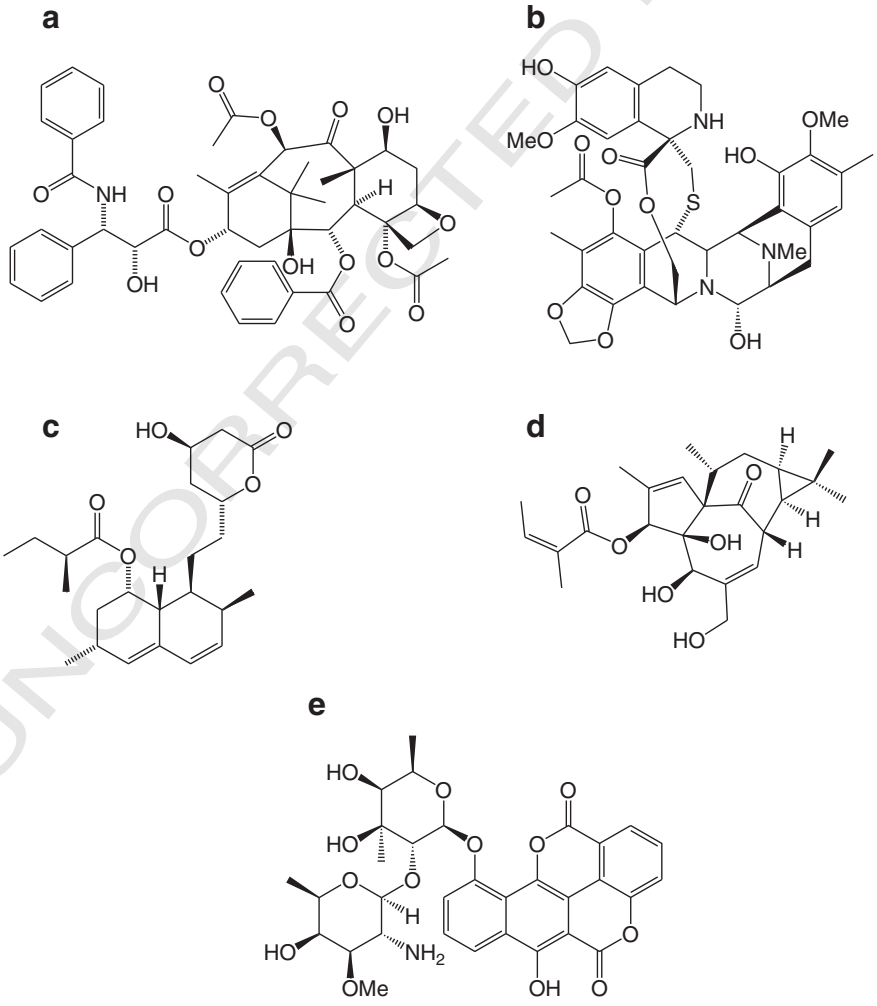

Fig. 1. Structures of some natural product based drugs from different organisms which are marketed or are under clinical trials: a — anticancer drug paclitaxel (Taxol®) produced from plants (*Taxus brevifolia* and its cell cultures); b — anticancer drug trabectedin (Yondelis®) produced from tunicate (*Ecteinascidia turbinata*); c — cholesterol lowering drug lovastatine biosynthesized from fungi (*Aspergillus* and *Penicillium* species); d — anticancer drug ingenol mebutate, which lead molecule ingenol is produced from plants (*Euphorbia peplus*, approved by the FDA in 2012); e — anticancer drug elsamicin A isolated from bacteria (*Actinomycetes* species) under Phase II clinical trials.

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