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Plant natural products: Back to the future or into extinction?

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Abstract

Natural product substances have historically served as the most significant source of new leads for pharmaceutical development. However, with the advent of robotics, bioinformatics, high throughput screening (HTS), molecular biology-biotechnology, combinatorial chemistry, in silico (molecular modeling) and other methodologies, the pharmaceutical industry has largely moved away from plant derived natural products as a source for leads and prospective drug candidates. Can, or will, natural products ever recapture the preeminent position they once held as a foundation for drug discovery and development? The challenges associated with development of natural products as pharmaceuticals are illustrated by the Taxol® story. Several misconceptions, which constrain utilization of plant natural products, for discovery and development of pharmaceuticals, are addressed to return natural products to the forefront.

Keywords: Plant natural products; Drug discovery; Agronomic production; Biomass

1. Introduction

Natural products have been investigated and utilized to alleviate disease since early human history. In the early 1900s, before the "Synthetic Era", 80% of all medicines were obtained from roots, barks and leaves. At that time, fluid extracts were in vogue. One pound of a crude botanical was percolated with a pint of alcohol, much as we make coffee today. "Take a teaspoonful of this before meals", the family doctor would say, perhaps adding that a mustard plaster or vegetable poultice would do no harm. Every household had its favorite tea and tonics. Trustful humanity placed its faith in the belief that for every ill there existed a cure in the plants of field and forest. As Rudyard Kipling wrote (1910), "Anything green that grew out of the mould was an excellent herb to our fathers of old." In more recent times, natural products have continued to be significant sources of drugs and leads. Their dominant role is evident in the approximately 60% of anticancer compounds and 75% of drugs for infectious diseases that are either natural products or natural product derivatives (Newman et al., 2003; Cragg et al., 2005). Despite this success, during the past couple of decades, research into natural products has experienced a steady global decline. The introduction of high-throughput synthesis and combinatorial chemistry with their promise of a seemingly inexhaustible supply of compound libraries has greatly contributed to this declining interest in the screening of natural products by the pharmaceutical industry.

2. Discovery and development from natural products

Some of the opportunities for natural products' discovery and development are in pharmaceuticals, agrochemicals, cosmetics, fine chemicals and nutraceuticals. The requirements for discovery, development and commercialization of pharmaceuticals are generally well known. The time required for development of pharmaceuticals ranges

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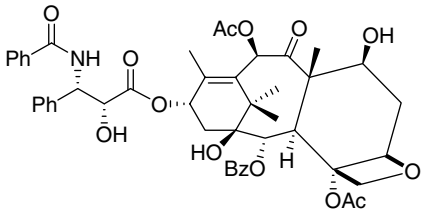

Fig. 1. Structure of paclitaxel (**1**).

from a few years to as many as 20 years. For example, the chemical structure of paclitaxel (**1**) (Taxol®) (Fig. 1) was reported and identified as the cytotoxic active constituent of extracts of *Taxus brevifolia* in 1971 (Wani et al., 1971). Taxol® (**1**) was approved for marketing as a cancer chemotherapeutic agent at the end of 1992, 20 years later. On average, new pharmaceuticals require a decade for development and commercialization. This timeframe has not changed appreciably in the last quarter century. The timeline for those activities are outlined in Fig. 2 (Tapestry Pharmaceuticals, 2006) and the length of each of the various phases are recorded in Fig. 3 (Basara and Montagne, 1994).

It is interesting that as information on the development of natural products is gathered, discussion of many of the important issues relative to natural products development is not found. Nowhere in this timeline is consideration given to supplying the quantity of drug needed for development, nor to developing a supply for commercial marketing. Those can be very challenging issues and are, we believe, the primary constraints on development of natural products as pharmaceuticals. These challenges are often viewed by pharmaceutical company executives as too limiting for the utilization of natural products (especially plant-derived natural products) for discovery and development

	Usual Range of Time Required (years)	Approximate Mean Time Required (years)
Stage of Development		
1. Project Formation to IND Filing	1.5 to 3.5	2.5
2. Phase I Clinical Studies	0.5 to 1.5	1.0
3. Phase II Clinical Studies	1.0 to 5.0	3.0
4. Phase III Clinical Studies and Preparation of NDA	1.0 to 5.0	3.0
5. FDA Review of NDA	1.0 to 5.0	2.5
Totals	5.0 to 20.0	12.0

Fig. 3. Typical time requirements to develop new drugs.

of new pharmaceuticals. The challenges must be identified and addressed if we are to return natural products to their preeminent position as the foundation of new pharmaceutical discovery and development.

3. Biodiversity and natural products

Pharmaceutical discovery is a numbers game. Thousands of chemicals must be evaluated to find a hit. The interesting agents that are identified as natural products derive from the phenomenon of biodiversity, i.e., the richness in variety of organisms in the ecosphere. A consequence of the interaction of this rich variety of organisms with each other and their environment is the evolution of diverse complex natural chemicals in the organisms that enhance their survival and competitiveness (Waterman, 1992). There are literally millions of natural chemical structure types resulting from nature's combinational chemistry

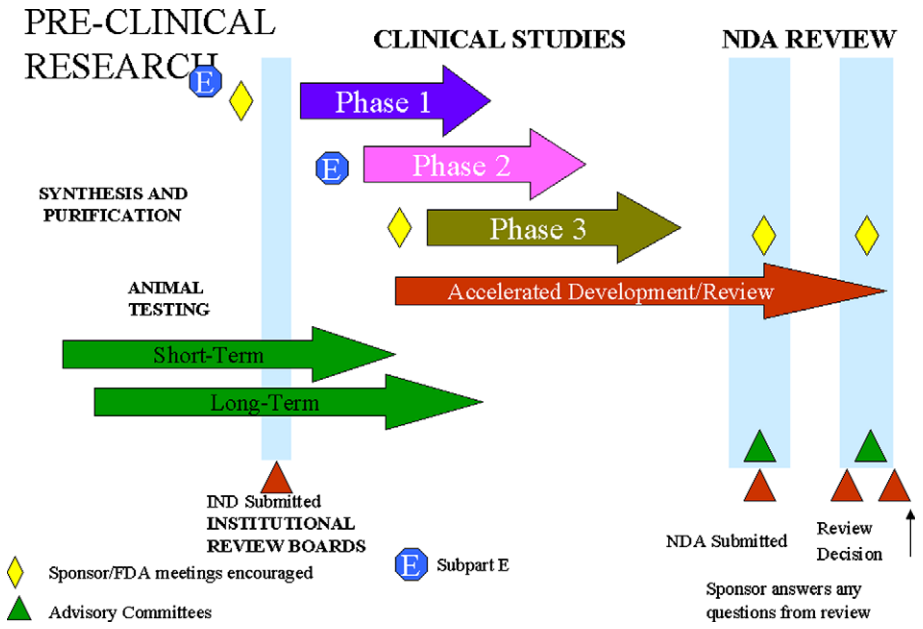

Fig. 2. Timeline for new-drug development.