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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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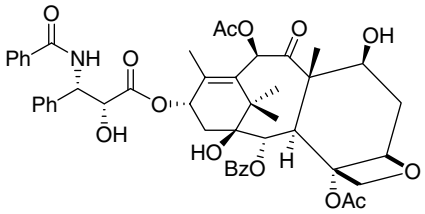

Fig. 1. Structure of paclitaxel (**1**).

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

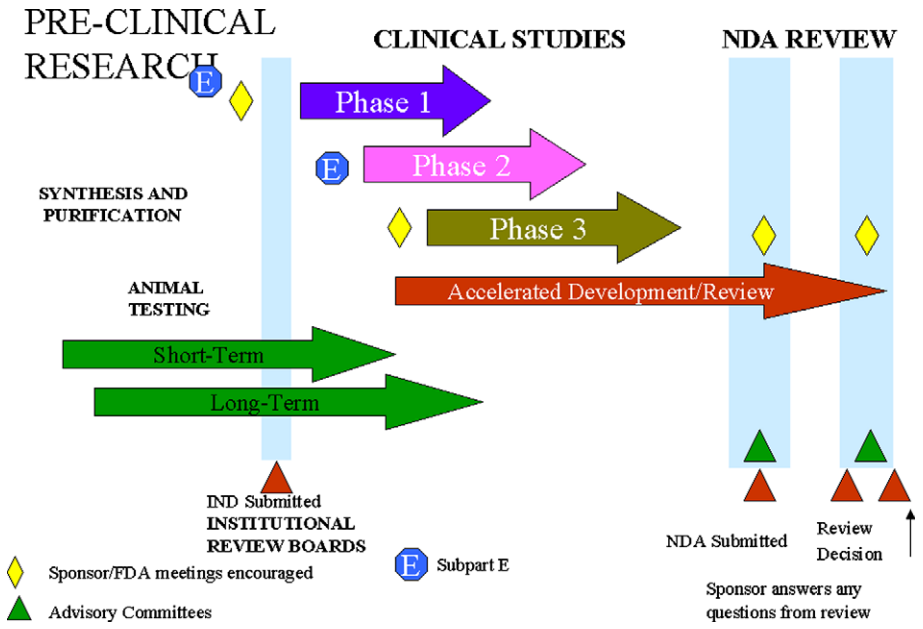

Fig. 2. Timeline for new-drug development.

effort supplying almost unimaginable chemical diversity, which yields stereochemically complex structures with diverse functional groups, molecules ideal for interacting specifically with biological target molecules. Importantly, nature has been ''doing'' combinational chemistry for eons, not just a decade or two, and has been selecting products from that combinational library that have specific biological advantage. Natural products researchers have not aggressively promoted natural product preparations in terms of nature's remarkable combinational chemistry numbers game. As Aristotle said, ''Nature does nothing without purpose or uselessly.''

4. Historic role of natural products in discovery of new pharmaceuticals

Natural product preparations have historically been the major source of pharmaceutical agents. Analysis of FDA new-drug approvals from 1981 to 2002 reveals that natural products continued to play a pivotal role during that time, even if the industry had turned to other discovery strategies (Newman et al., 2003). Indeed, more than 90% of current therapeutic classes derive from a natural product prototype and interestingly, even today, roughly two-thirds to three-quarters of the world's population relies upon medicinal plants for its primary pharmaceutical care (World Health Organization, 2002). Those ''medicinal plants'' are either preparations of or natural product substances from plants that have potential utility as pharmaceutical agents (Balunas and Kinghorn, 2005).

Historically also there were several problems associated with natural products (especially plant-derived products) that contributed to declining interest in their development within the pharmaceutical industry. Some years ago, there were significant difficulties with sourcing authenticated plant materials. It was easy to collect plants and demonstrate that their extracts had interesting biological potential. However, when researchers returned to confirm the potential and ultimately to carry out the development and commercialization of the product, failure often resulted because of inadequate documentation and loss of the original plant collections. There were also problems associated with the measurement of biological activities of natural product preparations, which ordinarily are complex mixtures of materials. Interactions among the components of the mixtures, either the antagonism by one material of another's activity or the addition or even synergy of activities, often gave very misleading results. Purification and identification of active constituents from complex natural product mixtures containing dozens to hundreds of different chemical substances, often of quite similar chemical and physical properties, were slow and not cost-effective. Once the active constituent was isolated and purified, its chemical structure still needed to be established. These issues are compounded in that natural products are often poor pharmaceuticals; their chemical stability may be marginal; they may have poor solubility or poor bioavailability characteristics; they may not formulate well, etc., therefore not adhering to Lipinski's Rule of Five (Lipinski et al., 1997). All of these issues have posed serious challenges. In our judgment, the issue most responsible for limited interest in plant derived natural products for pharmaceutical discovery and development has been concern over the availability of quantities of pure chemical substances. Quantities are required initially for generation of information to understand and assess real potential of the substance for pharmaceutical application. Ultimately, the most limiting consideration is the quantity required to meet market demand should a pharmaceutical become a successful drug in the market place. Market demand can reach a scale of hundreds to thousands of kilograms per annum. It is recognized that total synthesis will not economically provide the complex natural product to meet this market demand. We believe the problems mentioned above can be overcome.

5. The renaissance in natural products research

Natural products have pointed the way to the future. Many significant advances in science and industry have been inspired by the pursuit of capturing the value of natural products. Testaments to the role natural products have played in the evolution of organic synthesis are in *Classics In Total Synthesis* (Nicolaou and Sorenson, 1996) and *Classics in Total Synthesis II* (Nicolaou and Snyder, 2003) where all the synthetic targets are natural products. Efforts toward total synthesis of natural products have resulted in development of new synthetic methods (Wilson and Danishefsky, 2006), advances in the fields of medicinal chemistry, process chemistry and other aspects of the science of drug development and, of course, with provision of a continuous and reliable supply of new drugs to the pharmaceutical industry (Newman et al., 2003; Koehn, 2005; Ortholand and Ganesan, 2004; Paterson and Anderson, 2005). A number of advances in capability and technology are fostering a renaissance in natural products research and are directly or indirectly addressing the historical impediments to development of natural products (Brown and Newman, 2006; Fullbeck et al., 2006; Gomord et al., 2005; Jung, 2006; Koehn, 2005; Newman, 2006; Schuster, 2001; Tulp, 2004).

Perhaps the strongest impetus for development of new natural products is the advancement in bioassay technology over the last several years (Littleton et al., 2005; Piggot, 2004; Potterat, 2006; Rollinger et al., 2006). We now have highly automated, very specific and selective bioassays in which materials, including natural products preparations, can be evaluated quickly and economically. Indeed, advances in bioassay technology have been so great that the availability of substances for evaluation has become more limiting than the ability to carry out those evaluations. Once biological activity has been demon-

strated in an appropriate bioassay or primary screen, we now have available, based upon advances in separations and structure elucidation technology, the capability to isolate, purify and determine the chemical structure of the active constituent in a few days or, at most, a few weeks. The advances in separations technology are particularly associated with high performance chromatography methodologies (Foucault, 1995). Most recently, improved methodologies in countercurrent partition chromatography have further expanded the capabilities for separations (Berthod, 2002; Pauli, 2006). Structure elucidation technology has evolved particularly with the development of high field NMR spectrometry (Croasmun and Carlson, 1994; Claridge, 1999) as well as high-resolution technologies in mass spectrometry (Deng and Sanyal, 2006; Korfmacher, 2005). Most important are the two-dimensional NMR techniques that have been developed, which allow very rapid and straightforward assignment of structure to complex natural products. Additionally, the technologies of coupled liquid chromatography–mass spectrometry and similar techniques provide very potent and powerful methodologies for separation and structure elucidation (de Rijke et al., 2006; Niessen, 1999; Gross, 2006).

As increased understanding of biological and physiological pathways in all organisms is reached, much more specific and selective questions with regard to potential drug application can be formulated. An example of this is the investigation of substances that interact only with a very specific receptor rather than with a family of receptors. With the advances that have been made in biotechnology, those receptors can be cloned and "constructs" prepared in which cloned receptors become a component of a created cell line, which then ultimately forms the basis of a high throughput, very selective and specific bioassay. In this way, the advances in several areas can be used together to focus on the discovery of new substances as lead compounds for pharmaceutical development. Natural products represent the most important source of unique chemical substances for evaluation with these new assaying strategies for potential pharmaceutical utility.

Recognition that the biological diversity of the earth is rapidly diminishing also is fostering a renewal of interest in natural products research. Indeed, we cannot pick up a newspaper or news journal without encountering some article dealing with the rate, consequences, cause, etc., of loss of biological diversity. However, it must be emphasized that it is the loss of chemical diversity represented by those organisms that represents the true loss – the loss of possible benefit that those chemicals have for humankind. Even foodstuffs, building materials, fibers that are utilized to make clothing, etc., are chemicals derived from nature. The loss of those organisms and, in turn, the loss of the chemical diversity represented by those organisms, is a very important stimulus for natural products research.

Additionally, globalization of the world's economy serves as a stimulant for pharmaceutical development. The US pharmaceutical industry, at the moment, is still an important industrial leader worldwide. The recognition that through the discovery and development of new pharmaceuticals the competitive position of that industry can be maintained, leads to interest in natural products research as a way to increase the efficiency of discovery and development (Vuorela, 2004).

6. The utilization of the world's plants

It is generally estimated that there are approximately 300,000 species of higher plants (Lawrence, 1951). However, some report the number to be 250,000, others estimate the number to be as high as 500,000. The disparity in the numbers partly reflects a difference in philosophy among systematic botanists. It also reflects the more aggressive exploration of unusual environments, particularly diverse environments such as the tropical rainforests, where new species of higher plants are being encountered continually. Of the approximately 300,000 species of higher plants, about 1%, or roughly 3000, has been utilized for food. Of those 3000, about 150 have been commercially cultivated. In today's marketplaces throughout the world, unusual fruits and vegetables are beginning to appear because there is an increasing desire on the part of the world's populations for more "exotic" foodstuffs. However, the vast majority of caloric intake derives from about 20 species of plants. These plants represent the basis upon which the world's population is fed, representing a very narrow foundation supporting the world's human population.

On the other hand, approximately 10,000 of the world's plants have documented medicinal use – considerably more than the 3000 or so that have been utilized for food. Looking specifically at the utilization of plant materials in western medicine (the US, Western Europe, etc.), it is found that roughly 150–200 of such agents are incorporated. This is still a very small percentage of all higher plants. Thus, there are potentially many more important discoveries in the plant kingdom to be exploited for pharmaceutical application.

7. The perception that most limits interest in natural products

Concern over the availability of the quantity of a chemical entity required for development and market needs, has been the one most limiting factor for the pharmaceutical industry's interest in natural products. A realistic assessment of quantities of plant material required for the preparation of the amount of chemical substance necessary for the entire development process will address this concern.

To begin this assessment a "worst-case" scenario must be assumed. Under this scenario, the presence of an active product would be at a concentration of only 0.001% of dry weight of biomass. Current technologies are capable of identifying potential utility in the bioassay and of isolation

and characterization of the natural product that occurs in plant biomass at this low concentration. Identification of biological activity, isolation of active product and determination of chemical structure require at most 50 mg of the chemical substance (Cremin and Zeng, 2002; Eldridge et al., 2002). Isolation of this amount of chemical substance requires about 5 kg of dry plant material. At this point, with the chemical substance isolated and characterized and its biological properties determined, a decision point is reached: Is the chemical structure novel? Does this substance represent a potential new prototype? If the answers to these questions are "yes", we now have a natural product hit, and must decide whether to carry it forward into development.

Proceeding to the next step means assessing the real potential of the substance. Confirmatory bioassays must be carried out to make sure that the suspected biological activity is actually present. These must be followed with secondary biological assays to gain a full understanding of the breadth and selectivity of the biological activity and preliminary toxicology tests (if it cures a particular disease but kills the patient, then it is not really likely to be a drug substance). Once all of that information is available, some initial *in vivo* evaluation must be carried out to determine that the agent has real promise both in terms of its efficacy and its toxicity in a "real world" situation. To carry out these assessments, approximately 400–500 mg of pure active chemical substance is needed. That represents a 10-fold increase in the plant material required; as much as 100 kg of biomass (dry weight) is needed for processing to gain this additional information. This requirement is not particularly daunting, and it is very probable that development would proceed to this stage.

Success at this stage would suggest, then, that the agent would be carried forward into preclinical evaluation. This is where the quantity of dry biomass begins to look like a very daunting proposition. The quantity of pure chemical substance required for full preclinical development and a subsequent clinical trial is roughly 2 kg of pure product. Therefore, in the "worst-case" scenario for active product, (isolation yield from biomass of only 0.001%) 200,000 kg of dry plant biomass would be required to produce the required pure active product to this point.

Next, should the substance be carried forward through development and demonstrated to have true pharmaceutical value, what quantity of materials would be required to meet market need? Assuming that the agent would be utilized to treat an acute condition, that there existed a relatively small patient population of only about 10,000 patients per year and that approximately 2 g of the agent would be required for a course of therapy, 20 kg per year of bulk active drug would be required to meet the market need. Assuming again the "worst-case" scenario, 2×10^6 kg of dry biomass per year would be required. That may seem like a truly daunting or impossible quantity of material to collect and process.

However, considering this amount in the context of crop-based commodities, something that is more easily understood, this represents roughly 2200 tons of biomass, which is the equivalent of about 75,000 bushels of wheat, corn, soybeans or any other commodity. An average American farmer produces roughly this 75,000-bushel quantity or more each year. In this context, we are not talking about chopping down and processing entire tropical rainforests to obtain the 2×10^6 kg or more per year of dry plant biomass.

Let us consider another scenario, where the agent is used to treat a chronic condition, the patient population is considerably larger – 100,000 patients per year, and the agent has reasonable potency so that only ca. 50 mg per patient per day is required to treat the condition. Under these conditions, 2000 kg of bulk active drug would be required to meet the market need. Again assuming the "worst-case" scenario of 0.001% of active product isolated from biomass, 2×10^8 kg of biomass (dry weight) would be required to produce this 2000 kg per year of bulk active substance. The number, 2×10^8 kg, appears to be very large, but when placed again in the context of crop-based commodities such as wheat or corn or soybeans, it is obvious that this represents a modest production level. Indeed, many agricultural counties of the United States produce as much or more than the 7.5×10^6 bushels of a commodity that the 2×10^8 kg represent. In this context it is clear that this quantity of biomass is readily obtainable.

Two deliberately selected examples emphasize this point. Information on the worldwide production of marijuana and cocaine leads to the following observations: In 1996, an estimated 11,000 metric tons were produced worldwide with much of that produced in the United States (Goldberg, 2005). At a price of less than $2000 per pound, and considering all of the criminal penalties that would ensue if one were convicted of producing marijuana, it is clear that, when there is a market for a plant biomass, there will be an entrepreneurial effort to meet that market. Indeed, considering the billions of dollars spent each year to suppress drug plant production, it is easily appreciated that giving growers an alternate profitable and ethical crop to raise, will lead readily to the production of the necessary quantities of biomass for drug production to meet pharmaceutical application. In the case of cocaine, which is utilized as a nearly pure chemical entity (about $18,000 per kg at source) indeed a thousand tons, roughly one million kg, were produced worldwide in 1990 (National Narcotics Intelligence Consumers Committee, 1990), greatly in excess of the examples required to meet an ethical pharmaceutical market. Clearly, capability is present if there is a stable and bona fide market for the chemical substance. Finally, it should be noted that the "worst case" might not be representative. Natural product substances are often found in their plant source at 0.1% to even 1.0%, orders of magnitude greater than the "worst-case." Further selection can often raise concentration of the desired natural product in biomass to an even greater extent (Bruneton, 1999).

8. Meeting the supply challenge

If natural products are to be produced for utilization in the pharmaceutical industry, there will be certain criteria that a system of production must meet. First, it clearly must be economical. After all, if the drug costs hundreds to thousands of dollars per dose, there is no viable product. However, it should be noted that recently approved therapies for life-threatening conditions, cancer, stroke, etc., are often of such magnitude. Also, the production system must be sustainable and reliable. Patients will need the drug this year, next year and perhaps a decade from now, and a source of that agent must be available to meet those medical needs. And finally, today's society requires that production of natural products be environmentally safe, non-environmentally impacting. One cannot propose to cut down the rainforests or denude the earth of a particular species for the production of a natural product.

To meet these criteria and establish a viable production system, all the steps of production of a natural product must be systematically evaluated. First, a superior source of that substance must be identified. A strain or variety of the species must be discovered that has a high and consistent concentration of the natural product or a precursor of the natural product that can be converted economically by semi-synthesis to the final bulk active product.

Once that superior source has been identified, an uninterruptible and stable supply of that material must be secured (Khan, 2006). Ordinarily this means that an agronomic system for biomass production must be developed, i.e. one must bring the source into cultivation. This allows the full expression of the genetic capability of the cultivar. Climate and soil types must be matched to the requirements of the plant; the impact of fertilization, irrigation, etc., on the production of the biomass and its chemical constituents must be understood; and, generally, the economical growth and cultivation of the material must be explored. In the future, a plant's production of secondary substances may be controlled with growth regulators of one sort or another. Finally, Good Agriculture Practices (i.e., "GAP") (World Health Organization, 2003) should be utilized in this agronomic production.

The successful development of biomass production will dictate development of appropriate harvest techniques. Topics to consider are determination of maximum concentration of active drug product in the plant during the growing season and the handling of freshly harvested biomass to retain drug content. And finally, in order to maintain an economic system of production, mechanization of the harvest process must be addressed.

Harvested biomass will require an economic processing facility that is capable of processing biomass for isolation of the active product over an entire calendar year, not just immediately after harvesting. Therefore, technology must be developed to stabilize the biomass so that it retains drug content during storage before its ultimate processing. This will usually involve developing an appropriate drying process.

Once processing of the biomass is initiated, the extraction–purification system must be economical; it must be efficient in its recovery of the natural product from the biomass. It must be safe in its operation, and the generation of waste products must be minimized so that there is no deleterious environmental impact from the processing of the biomass material. When systematic evaluation of a production strategy for natural products is carried out, there is evidence that the quantity of natural product substance does not become a limitation either in development or ultimate commercialization of pharmaceuticals derived from natural products.

This point may be illustrated with the example of Taxol® – an anticancer agent of plant origin (Suffness, 1995). Taxol® was initially discovered through the NCI program for evaluation of plant preparations for anticancer activity (Kingston et al., 1993; Suffness, 1995). In 1962, USDA botanist Arthur Barkley collected *Taxus brevifolia* and submitted that biomass to the NCI's anticancer evaluation effort. In 1964, an extract of the bark was shown to be highly cytotoxic *in vitro* to cancer cells. This material was re-collected and the biological activity was confirmed in certain animal models of cancer. By 1967, 3000 pounds of bark were collected and processed, leading, in 1971, to the structure elucidation of Taxol® (Wani et al., 1971). Efforts by Susan Horowitz (Suffness, 1995) in the late 1970s showed that Taxol® had a unique mechanism of action in its suppression of the growth of cancer cells. In 1977, this led to its extensive evaluation in animal models of cancer where it showed high activity and led to its designation for development. In 1983, Taxol® entered human clinical trials. By 1988, initial clinical results in ovarian cancer were very encouraging and a major effort was initiated. This was followed by the development of a system for the economic production of Taxol® and final development for approval for utilization in the treatment of cancer. In 1992, Taxol® was approved for the treatment of refractory ovarian cancer. In 1993, Bristol-Myers Squibb Company had sales of more than $150 million of Taxol®. BMS sales of Taxol® grew to nearly $2 billion, by 2000, when Taxol® became generic (www.cancerpage.com/news/article.asp?id = 4866). Thus, it can be seen that this very complex natural product of plant origin has great utility in the treatment of human cancer and that because of its complex chemical structure, it will not likely be economically prepared by synthesis. Consequently, we must rely on isolation from a natural source of the agent or a natural product semi-synthetic precursor. Indeed, Bristol-Myers Squibb evolved a system of production based upon isolation of a precursor of Taxol® from the leaves or needles of cultivated *Taxus baccata* or *T. wallichiana* that will provide the hundreds of kilograms of Taxol® required per year for the future treatment of cancer patients (Jacoby, 2005).

9. Conclusion

Plant derived natural products hold great promise for discovery and development of new pharmaceuticals. Careful consideration of the entire process of discovery and development – a ''systems'' approach – will be required to realize this great promise effectively. While it is recognized that each solution to the supply issue may seem to be a specific case, we believe all solutions really represent variations on the theme and can be effectively identified and implemented by a systematic endeavor. The perceptions limiting interest in the utilization of plant derived natural products can be readily addressed to return them to their preeminence in pharmaceutical discovery and development.

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