

# Recent Advances in the Discovery and Development of Plant-derived Chemotherapeutic Agents

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**Abstract:** Plants have long served as traditional herbal medicines, and natural products make excellent leads for new drug development. New plant-derived medicines can come from three sources: single active principles, active fractions, and validated prescriptions. Conventionally, for single active compounds, lead discovery and drug development involve highly efficient bioactivity-directed fractionation and isolation (BDFI) coupled with structural characterization, analog synthesis, and mechanism of action studies. Today, new scientific technologies, including tissue culture and biological screening methods, continue to improve this process. For multi-component herbal prescriptions, standardization and quality control, including GAP (Good Agricultural Practice), GMP (Good Manufacturing Practice) and GCP (Good Clinical Practice), must be performed to guarantee high quality and consistency. In addition, reliable chemical, pharmacological, as well as drug administration, distribution, metabolism, excretion, and toxicological (ADMET) studies are needed to validate herbal efficacy and safety. This talk will discuss the principles listed above, particularly focusing on the successful development of anti-cancer and anti-HIV clinical trials candidates from numerous bioactive compounds discovered in the author's Natural Products Laboratory. Continued exploration of under-investigated plant species should guarantee bright prospects for sustained discovery and development of new medicines for this century.

**Keywords:** chemotherapeutic agents; plant-derived bioactive compounds; antitumor agents; anti-HIV agents.

## 1. Introduction

Plants generate bioactive compounds as part of their own "defense mechanisms" against plant pathogens [1] – accordingly, it is only fitting that plant-derived natural products and their analogs account for more than 50% of all clinically used drugs, with ca. 25% from higher plants [2]. People from all cultures have traditionally relied on natural resources,

predominantly of plant origin, as herbal folk medicines, including for example, the analgesic morphine, the cardiotoxic digoxin, the antimalarial quinine and the antineoplastic vincristine.

This history clearly implies that herbal medicines will continue to play a role in the modern discovery and development of new drugs. The principal concepts of this process are shown in Figure 1 below [3].

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As suggested in this figure, not only single active principles (single herbal-derived compounds), but also active fractions (herbal extracts) or validated and improved prescriptions (multiple herbal products) can be investigated for new drug discovery. However, issues that should be addressed by transferring herbal medicines from folkloric to mainstream international pharmaceutical use are supply, quality control, safety, and proven ef-

ficacy. High quality, batch-to-batch consistency, and efficacy/safety must be guaranteed using stringent quality control measures including GAP (Good Agricultural Practice), GMP (Good Manufacturing Practice) and GCP (Good Clinical Practice), at each step in the development of standardized new medicines (single or multi-component) from herbal medicine as shown in Figure 2.

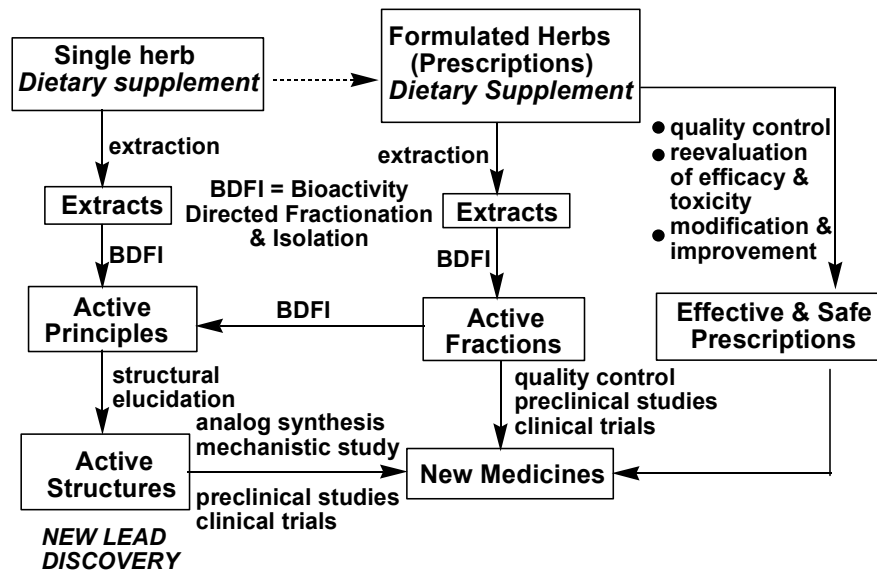


Figure 1. Principal concepts of research on new medicines

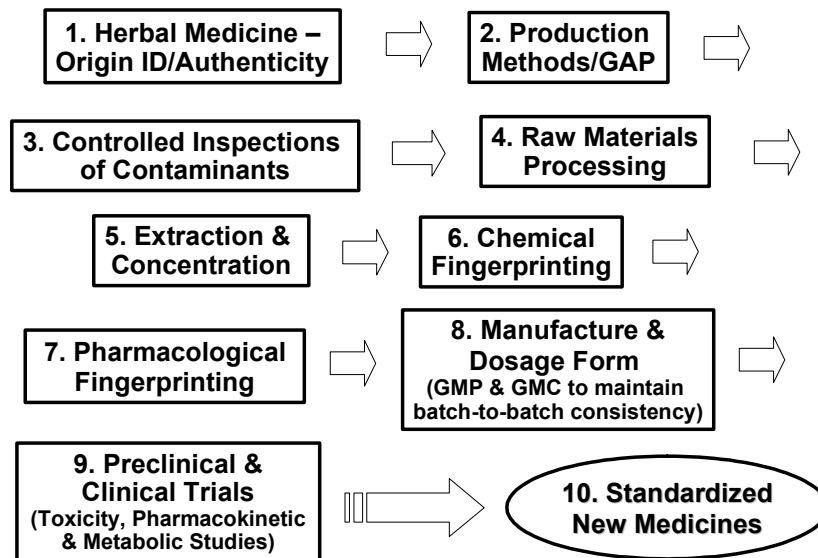


Figure 2. Quality control for standardized new medicines

In the author's and other natural product laboratories, lead discovery through bioactivity-directed fractionation and isolation (BDFI) of bioactive natural lead compounds is followed by a cyclical process of drug optimization, which includes design, synthesis, screening and analysis of improved analogs using structure-activity relationship, mecha-

nism of action, drug metabolism, molecular modeling, and parallel syntheses studies, as well as other preclinical studies, such as drug administration, distribution, metabolism, excretion, and toxicological (ADMET) studies, and clinical trials. A diagram showing the stages and strategies in preclinical drug discovery and development is shown in Figure 3.

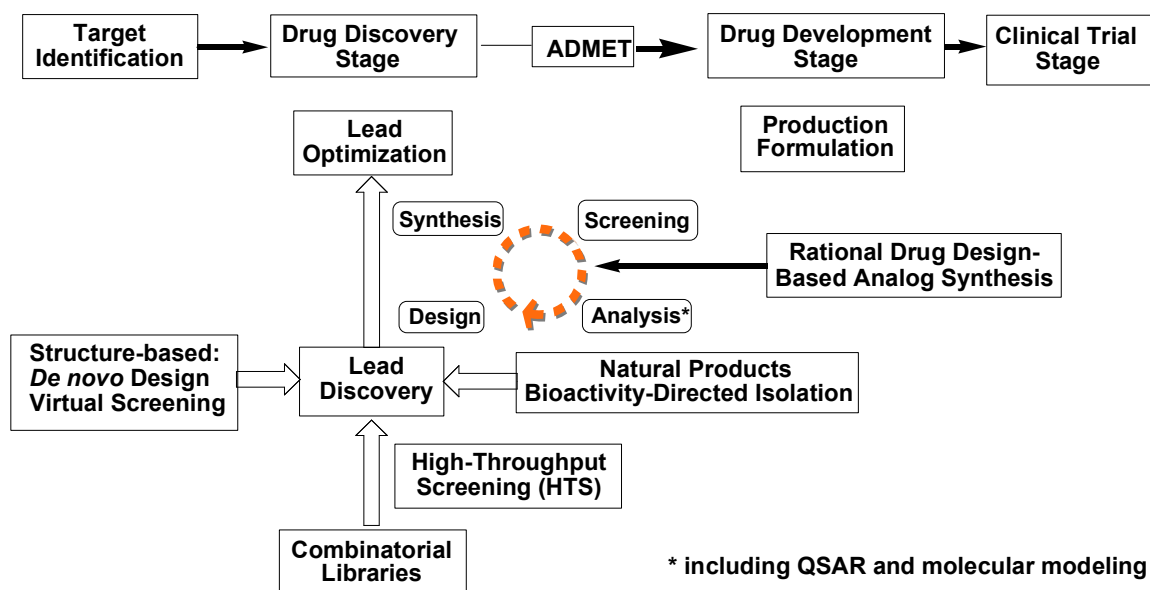


Figure 3. Stages and strategies in preclinical drug discovery and development

Numerous examples could be given of natural plant products and their analogs still used as medicines, including the antiasthmatic ephedrine [from *Ephedra sinica*, Ma-Huang, a primary component of a traditional Chinese medicine (TCM) used to treat bronchial asthma, cold and flu, cough and wheezing, fever, chills, lack of perspiration, headache, and nasal congestion] and the antimalarial artemisinin (from *Artemisia annua*, Qing Hao, used in a folkloric tea to cure malaria fever). Following in the footsteps of such discoveries, the author's Natural Natural Products Laboratory (NPL) has discovered numerous diverse natural products from herbal sources and optimized them to clinical trials candidates [4]. One notable example in the anti-cancer field is the chemical modification of

the natural product podophyllotoxin [the cytotoxic principle of *Podophyllum emodi* (Kuei Chiu), which is listed in the Chinese herbal classic "Shen Nung Pen Tsao Ching"] to the patented clinical trial candidate, GL-331 (1, Figure 4), a  $4\beta$ -(*p*-nitrophenylamino)-4'-demethyl analog of podophyllotoxin [5]. GL-331 showed good antitumor efficacy in initial anticancer clinical trials at the M.D. Anderson Cancer Center [6]. Compared with the clinically used etoposide, which is also a chemically modified podophyllotoxin analog, GL-331 shows evidence of activity in refractive tumors and the ability to combat the enormous problem of drug resistance. The NPL continues to use modern scientific technology including computational modeling studies [most recently k Nearest Neighbor

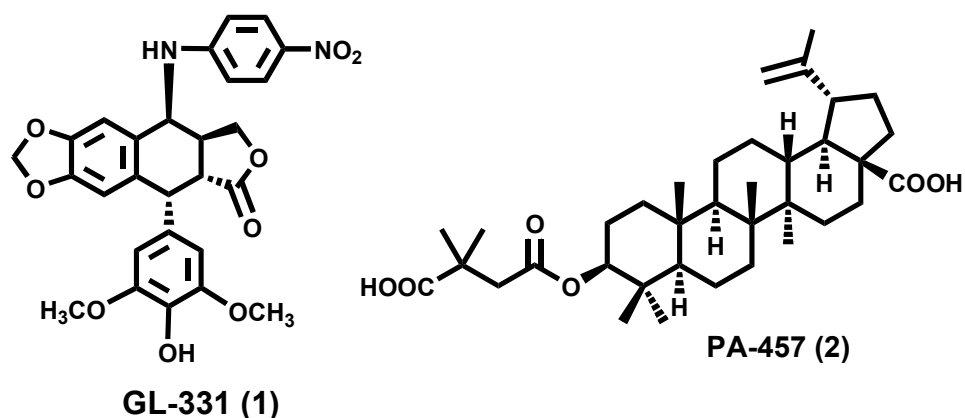
(kNN) QSAR] [7, 8], which has led to additional promising candidate compounds.

Another significant research highlight from the NPL is PA-457 (2, Figure 4), which was developed from the natural triterpene betulinic acid, isolated by BDFI as an anti-HIV principle from a Formosan medicinal plant *Syzigium claviflorum* (Pang Hua Chih Nan) through BDFI [9]. PA-457 is in “fast-track” new drug development as an anti-HIV drug. It has successfully completed Phase IIa randomized double-blind clinical trials, showing potent antiviral activity. Phase IIb and III studies are slated for 2006. In addition to high efficacy, PA-457 disrupts the late-stage viral maturation of the viral gag protein, producing defective and noninfectious virus. It is classified as the first anti-HIV maturation inhibitor – a mechanism not shared by any current approved anti-AIDS drug [10, 11]. Thus, PA-457 is an ideal candidate to address the growing problem of viral drug resistance, the primary

cause for antiretroviral treatment failure.

Most recently, advances in the discovery and development of plant-derived chemotherapeutic agents have been assisted by new scientific technologies, including new production technologies, such as tissue culture methods [12], new design technologies, such as computer modeling as mentioned above, and new developmental technologies, such as nanometer technology, proteomics and metabolomics [13]. New automated biological screening methods are also increasing the speed and efficiency of plant-derived new drugs discovery and development. The future of plants as modern pharmaceuticals is indeed bright as only a small (5-15%) percentage of existing higher plants have been thoroughly evaluated for new drug leads.

By addressing the three required criteria of efficacy, safety and batch-to-batch consistency, both single and multi-component herbal plant products will surely be a continued source of world-class new medicine.



**Figure 4.** Structures of **GL-331** and **PA-457**, plant-derived clinical trials candidates discovered in the NPL, for potential treatment of cancer and AIDS, respectively.

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