



Reverse Pharmacology Applicable for Botanical Drug Development – Inspiration from the Legacy of Traditional Wisdom

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Ethnopharmacology and Traditional Herbal Medicine

Over the past two decades, traditional medicine, now termed “Complementary and Alternative Medicine (CAM)” in the medical community, has been attracting considerable attention. CAM has opened an important genre of the comprehensive and integrative health care provision and health sector reform. An essential part of CAM includes practice of herbal medicine which employs diverse botanical formulations with distinct pharmacological properties. Plant-derived substances have been the mainstay of traditional medicine and represent a principal components of the modern pharmaceuticals as well. In reality, drugs derived from natural product resources, especially those in plant kingdom, are of immense importance in terms of their potential applications for the management of a multiplicity of human disorders. Thus, a substantial proportion of all prescriptions dispensed from community pharmacies in the world contain one or more ingredients derived from higher plants. It is estimated that approximately 80% of the world’s population depends exclusively on plants for their health and healing. In the area of cancer over the time frame around 1940s to 2007, of the 155 small molecules, 73% are non-synthetic, with 47% actually being either natural products or directly derived therefrom (Newman and Cragg, 2007).

A wide array of modern drugs included the international pharmacopoeia have an origin in ethnopharmacology and traditional herbal medicine. Numerous plant extracts and their ingredients have unique pharmacological activities, such as anti-inflammatory, anti-diabetic, anti-carcinogenic, vasodilatory, anti-bacterial, anti-viral, anticonvulsant, sedative and antipyretic effects. However, very few randomized-controlled studies have been carried out to precisely evaluate their therapeutic efficacy and safety. Nonetheless, for some of the botanical materials, there are relatively well-organized database available describing the therapeutic potential, and their active ingredients can be tested by exploiting modern scientific methods (Patwardhan and Vaidya, 2010).

In the early days of pharmacology, therapeutic drugs were often discovered incidentally from medicinal plants as part of folk remedy. These desirable accidental discoveries are referred to as drug serendipity (Takenaka, 2001). There are many examples of medicinal plants and their constituents that have provided serendipitous bedside observations. Such clinical hits can be a basis of drug discovery and development. Advances in combinatorial chemistry and systems biology have created many drugable new entities.

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Paradigm Shift for Modern Drug Development: Reversing the Path

Biotechnological advances, including high throughput screening or combinatorial and asymmetric synthesis, have opened new vistas in drug discovery. Nonetheless, the industry is facing serious challenges as the drug discovery process has become extremely expensive, riskier and critically inefficient. Post-marketing failures of blockbuster drugs and a serious innovation deficit are major concerns of big Pharmas. Consequently, there has been a remarkable shift in favor of single- to multi-targeted drugs, especially for polygenic syndrome, based on knowledge from traditional medicine. Strategic options based on natural product drug discovery, ethnopharmacology and traditional medicines are re-emerging as an alternative discovery engine (Patwardhan and Vaidya, 2010). Scientifically validated and technologically standardized botanical products may be explored on a fast track using innovative approaches (Patwardhan et al., 2008). This offers an efficient development platform for herbal formulations, which expedites the process for the botanical drug discovery and development by reducing and economizing investments (Patwardhan and Vaidya, 2010).

A trans-disciplinary endeavor called reverse pharmacology has recently emerged and this new academic discipline can reduce three major bottlenecks—cost, time, and toxicity—frequently encountered in conventional drug development. Reverse pharmacology offers a major paradigm shift in drug discovery. Instead of serendipitous findings pursued randomly, an organized path from clinical experiences, experimental observations and data base has been established (Patwardhan et al., 2008). Traditional knowledge and clinical observations, combined with powerful modern technologies revolutionize the whole process of drug discovery, design and development.

Reverse Pharmacology

Reverse pharmacology integrates documented serendipitous clinical and experimental hits into leads that are further developed into drug candidates or formulations through more systematic and precisely designed preclinical and clinical research. A salient feature of this approach is the combination of knowledge learned from traditional or folk medicine and the modern technology to provide better and safer leads (Patwardhan and Mashelkar, 2009). The endeavor to study well-documented findings would

facilitate not only identification of candidate drugs but also understanding of their underlying molecular mechanisms.

Drug screening using the classical pharmacological methods is time-consuming and inefficient. Using current technology and genomics, proteomics and metabolomics, scientists now move in the opposite direction to that used in conventional pharmacological research for new drug development. This strategy, referred to as “reverse pharmacology”, has many advantages. The drug development process with reverse pharmacological approach is much faster (< 5 years) and more efficient than that achievable with the classical approach, which often requires the decade-long time to launch (Takenaka, 2001).

Reverse pharmacology can be perceived to comprise of three domains. The first one is the experiential phase that includes documentation of robust clinical observations of the biodynamic effects of formulations used in folk medicine or already developed drug formulations and their precursors by meticulous record keeping. Second, the exploratory studies for tolerability, drug-interactions, dose-range finding in ambulant patients with defined subsets of the disease and para-clinical studies using relevant *in vitro* and *in vivo* models to evaluate the target-activity. Third phase includes experimental studies, basic and clinical, at several levels of biological organization, to identify and validate reverse pharmacological correlates of safety and efficacy of drug candidates. The traditional knowledge-inspired reverse pharmacology relates to reversing the routine “laboratory-to-clinic” path of drug discovery pipeline to “clinic-to-laboratories” (Patwardhan et al., 2008)

Conclusion and Future Perspectives

Drug discovery strategies based on natural products and traditional medicines are re-emerging as attractive options. The R&D thrust in many pharmaceutical sectors has focused on development of botanical drugs through investigation of leads from the traditional herbal medicine. Herbs are of great importance as a reservoir of chemical diversity and can be explored for discovery of potential drug candidates. Knowledge and experimental database of traditional herbal medicine can provide new functional leads to reduce time, money and toxicity – the three main hurdles in the conventional drug development. A reverse pharmacology approach, inspired by traditional medicine, can offer a rational

and pragmatic strategy for identification of new drug candidates. Reverse pharmacological approaches rely primarily on clinical experiences, observations or available data on actual use in patients as a starting point. This trans-disciplinary science also adopts principles of systems biology where holistic yet rational analysis is done to address multiple therapeutic requirements. Since safety of the materials has already been established from traditional use track record, pharmaceutical development, safety validation and pharmacodynamic studies can be conducted in parallel to controlled clinical studies. Thus, drug discovery based on the reverse pharmacology follows a path from clinics to laboratories, an opposite direction applied for conventional synthetic drug development (Patwardhan et al., 2008)

Legacy of traditional wisdom, modern Western medicine and high throughput technology converge to form a golden triangle. By bringing all these together, reverse pharmacology can accelerate the development of innovative drugs with excellent efficacy with minimal toxicity.

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