

Perspective paper

Ethnopharmacology and drug discovery

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Abstract

Ethnopharmacology and natural product drug discovery remains a significant hope in the current target-rich, lead-poor scenario. Many modern drugs have origin in traditional medicine and ethnopharmacology. Traditional Indian Medicine – Ayurveda has a long history and is one of the great living traditions. Considerable research on pharmacognosy, chemistry, pharmacology and clinical therapeutics has been carried out on Ayurvedic medicinal plants. Several preclinical and clinical studies have examined cytoprotective, immunomodulatory and immunoadjuvant potential of Ayurvedic medicines. The ethnopharmacology knowledge, its holistic and systems approach supported by experiential base can serve as an innovative and powerful discovery engine for newer, safer and affordable medicines.

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1. Impasse

Traditions are dynamic entities of unchanging knowledge. Traditional medicine is in an evolutionary process as communities and individuals continue to discover new techniques that can transform practices. Ethnopharmacology and drug discovery using natural products remain important issues in the current target-rich, lead-poor scenario (Patwardhan et al., 2004). Many modern drugs have their origin in ethnopharmacology. However, despite technological advances, the drug discovery process is facing a major innovation deficit that is adversely affecting the pharmaceutical industry. Many recent studies suggest that entry barriers have fallen over time for new drug introductions (Di Masi and Paquette, 2004). The development histories of entrants to new drug classes suggest that development races better characterize new drug than does a model of post hoc imitation. Thus, the usual distinctions drawn between breakthrough and me-too drugs may not be very meaningful. The pharmaceutical industry has not been as innovative as it claims to be and the regulatory processes are adding more risk and years to the discovery cycle and it

is predicted that the worst is yet to come. On one side, it has become technology intensive and high throughput yet on the other side has remained very low throughput in originality. Drug companies actively research for new ways to detect interactions with known receptors and seek out new receptors. But the development task is getting increasingly difficult and taking extensive cost due to post-approval or post-marketing withdrawals. All these problems are obviously reflecting on the costs of the drugs that are rapidly increasing and becoming unaffordable to the majority of the population both from the developed as well as poor and developing countries. Moreover, protection of traditional knowledge in relation to health, medicine and biodiversity is becoming a great concern. To resolve this impasse, pharmaceutical companies are now looking for true innovative approaches to drug discovery. The World Health Organization has newly established a Commission on Intellectual Property, Innovation and Public Health to address these issues critically (Patwardhan, 2005c).

2. Ayurveda

Ayurveda and Chinese medical systems are great traditions and have an important role in bioprospecting of new medicines. A considerable amount of research on

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pharmacognosy, chemistry, pharmacology and clinical therapeutics has been carried out on Ayurvedic medicinal plants (Patwardhan et al., 2004). Numerous molecules have come out of Ayurvedic experiential base, including *Rauwolfia* alkaloids for hypertension, psoralens for vitiligo, *Holarrhena* alkaloids in amoebiasis, guggulsterons as hypolipidemic agents, *Mucuna pruriens* for Parkinson's disease, piperidines as bioavailability enhancers, baccosides for mental retention, picrosides for hepatic protection, phyllanthins as antivirals, curcumines for inflammation, withanolides and many other steroidal lactones and their glycosides as immunomodulators (Patwardhan, 2000). Ayurveda (Ayur: Life; Veda: Science) means science of life in *Sanskrit* and aims at holistic management of health and disease. It remains one of the most ancient medical systems widely practiced in the Indian subcontinent and has a sound philosophical, experiential and experimental basis. *Charak Samhita* and *Sushrut Samhita* (100–500 B.C.) are main Ayurvedic classics, which describe over 700 plants along with their classification, pharmacological and therapeutic properties. Rasayana therapy is one of the eight branches of Ayurveda and generally consists of nourishing and rejuvenating drugs with multiple applications for longevity, memory enhancement, immunomodulation and adaptogenic. Many researchers have supposed the neuro-endocrine immune axis theory to explain Rasayana activity and they have considered it to be an innovative source of immunodrugs (Patwardhan, 2005a,b).

3. Research

We have been studying some selected Rasayana, such as *Withania somnifera* (Ashwagandha), *Asparagus racemosus* (Shatavari), *Tinospora cordifolia* (Guduchi), *Phyllanthus embellica* (Amalaki) and *Semecarpus anacardium* (Bhalsataka). As a representative example, a brief research review is given here on *Withania somnifera* (WS), which is also known as Indian ginseng and winter cherry. Major bioactive constituents of WS root are steroidal alkaloids and lactones known as withanolides. Several preclinical studies have examined cytoprotective, immunomodulatory (Ziauddin et al., 1996; Agarwal et al., 1999) and immunoadjuvant potential (Gautam et al., 2004a,b) of WS. The plants exhibited modulatory effects on cytotoxic lymphocytes production leading to reduced tumor growth. WS treatment in normal and tumor bearing mice showed in a positive influence on natural killer cells activity resulting in enhanced cell killing (Diwanay et al., 2004). In a comparative pharmacological investigation of WS and Ginseng, the WS treated group showed better anabolic and antistress activity than Ginseng with additional anti-inflammatory activity (Grandhi et al., 1994). Clinical studies on WS have shown moderate analgesic, anti-inflammatory and disease modifying activity in experimental animals (Saraf et al., 1989) and arthritis patients (Chopra et al., 2004). Better understanding of basic principles of Ayurveda and harmonization of various

practices will need new algorithms and programs for strengthening decisions with a system in practice (AyuSoft, 2004). The whole person concept of Ayurveda and the Prakriti relevance in therapeutics indicate strong genetic connotation and can form basis of pharmacogenomics and customized medicine (Patwardhan, 2005c).

4. Innovation

Globally, there is a positive trend in favor of traditional and integrative health sciences both in research and practice. There are common approaches to drug discovery including use of chemical biology, serendipity, chemical synthesis, combinatorial chemistry and genomics. However, the innovative approaches involve ethnopharmacology, reverse pharmacology, holistic, systems biology and personalized medicine.

There are clear trends to show that the mainstream in pharmaceutical research is moving away from single molecule or single target approach to combinations and multiple target approaches (Wermuth, 2004). The ethnopharmacology knowledge and experiential base allows drug research from 'Clinics to Laboratories'—a true Reverse Pharmacology Approach (Vaidya, 2005). In this process, 'safety' remains the most important starting point and the efficacy becomes a matter of validation. A golden triangle consisting of Traditional Knowledge, Modern Medicine and Modern Science with systems orientation will converge to form an innovative discovery engine for newer, safer, affordable and effective therapies (Mashelkar, 2005). In India, efforts in these directions are underway to establish pharmacoepidemiological and experimental evidence-base for new chemical/molecular entities and development of standardized herbal formulations under the Council for Scientific and Industrial Research and Government of India's New Millennium Indian Technology Leadership Initiative.

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