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REVIEW ON REVERSE PHARMACOLOGY

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ABSTRACT

Traditional medicines emerged as a boon for the populations with strong socio-cultural and historical influences or in the absence of alternative or complementary therapies. Ayurveda, an Indian system of medicine, built remarkable knowledge over the practice of several thousands of years. This gold mine of clinical observations is attracting global pharmaceutical corporations to fuel their investigational drug pipelines. (1)

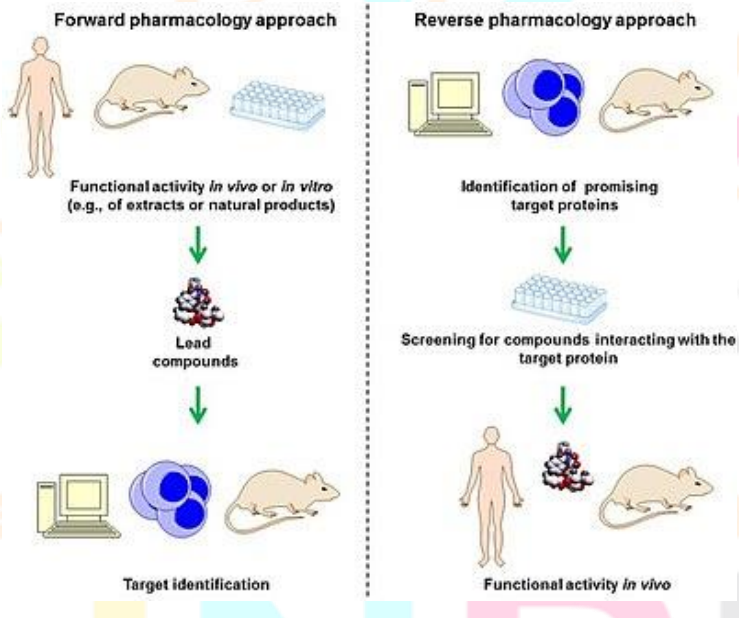
Reverse pharmacology (RP) is a trans-disciplinary path for drug discovery and development from bedside observations on drug effects to bench-side experiments. This approach generates evidence of safety and efficacy at different levels of biological organization, ranging from cell to community. Eventually the innovative integration of research methods will be translated back to the bedside as a new drug. The experiential wisdom of traditional systems like Ayurveda is scientifically explored by systematic RP. This is meant to enrich modern medicine, by the relevant application of the drug discovery sciences. The evidence by RP would also help to rationally understand Ayurveda. This article highlights how the bedside experience in arthritis has been translated by RP into evidence by defined experimental and clinical studies. There is a need to understand and apply the basic principles and practices of Ayurveda in the specific protocols and models in RP so as to truly integrate effective and safe usage for definite indications.(2)

Keywords: Ayurveda, Traditional medicines, repurposing drug, reverse pharmacology.

INTRODUCTION

Reverse pharmacology, is defined as the science of integrating documented clinical experiences and experiential observations into leads, through transdisciplinary exploratory studies, and further developing these into drug candidates through robust preclinical and clinical research.

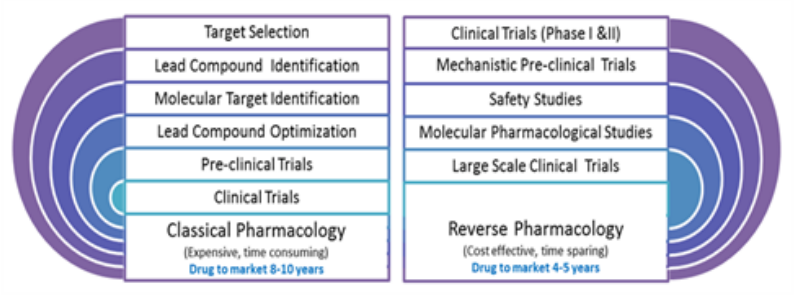
In the field of drug discovery, reverse pharmacology[I] also known as target-based drug discovery (TDD), a hypothesis is first made that modulation of the activity of a specific protein target thought to be disease modifying will have beneficial therapeutic effects. Screening of chemical libraries of small molecules is then used to identify compounds that bind with high affinity to the target. The hits from these screens are then used as starting points for drug discovery. This method became popular after the sequencing of the human genome which allowed rapid cloning and synthesis of large quantities of purified proteins. This method is the most widely used in drug discovery today. Differently than the classical (forward) pharmacology, with the reverse pharmacology approach *in vivo* efficacy of identified active (lead) compounds is usually performed in the final drug discovery stages.(3)



Difference between Ayurveda and modern medicine

"Ayurveda is natural and safe" and "modern medicine is harmful" are deeply embedded perceptions. Modern medicine is overwhelmingly strong in emergency clinical situations

Every day, potential new medicines are being researched and developed in various parts of the world. The identification of these potential new drugs is done through a vigorous process known as the drug discovery process. The drug discovery process can be divided into two opposing approaches, which are the classical pharmacology and the reverse pharmacology (4-5)



Differences in pathways of classical and reverse pharmacology.

In Ayurvedic pharmacology, physiological and biochemical effects of drugs and their mechanism of action in the body are explained with the help of pharmacodynamic principles, namely, rasa (taste), guna (qualities), virya (potency/energy), vipaka (biotransformation), and prabhava (empirical/inexplicable principle)

History:

India • Sir Ram Nath Chopra and Gananath Sen laid the foundation of reverse pharmacology of ayurvedic drugs. The credit for stimulating interest of Indian chemists and pharmacologists in medicinal plants should go to Sir Ram Nath Chopra who has been acclaimed as the 'Father of Indian Pharmacology[(6)]

The father of modern pharmacology is Oswald Schmiedeberg (1838–1921) is generally recognized as the founder of modern pharmacology. The son of a Latvian forester, Schmiedeberg obtained his medical doctorate in 1866 with a thesis on the measurement of chloroform in blood. He worked at Dorpat under Buchheim, succeeding him in 1869.

The reverse pharmacology described here relates to reversing the *laboratory-to-clinic* process of discovery, to one of *clinics-to-laboratories*. This is known as reverse pharmacology, which is defined as the science of integrating documented clinical experiences and experiential observations into leads, through transdisciplinary exploratory studies, and further developing these into drug candidates through robust preclinical and clinical research. In this process, *safety* remains the most important starting point, and efficacy becomes a matter of validation.

Reserpine, an alkaloid isolated from *Rauwolfia serpentina*, also known as Indian snakeroot, was a major discovery made by using the reverse pharmacology approach. In 1931, Indian chemists Sen and Bose convincingly demonstrated the antihypertensive and tranquillizing effects of the plant. They also observed unique side effects, such as depression, extra pyramidal syndrome, gynecomastia, and other side effects. Later, in 1949, Rustom Jal Vakil, who pioneered the development of cardiology in India, published a trial of *Rauwolfia* on patients with essential hypertension, which reported a reduction in systolic and diastolic blood pressure. It took decades to delineate the mechanisms of these side effects. This effort led to a watershed for new antidepressants, anti-Parkinson's disease drugs, and prolactin-reducing drugs. Reserpine as an antihypertensive alkaloid became available in the market as a result of work carried out by Ciba–Geigy. This was probably the first time the principles of reverse pharmacology were systematically used for focused, fast-track drug discovery based on Ayurveda knowledge.

Reverse pharmacology was practiced for several years at Ciba–Geigy and Podar Ayurveda Hospital, Mumbai. Some promising work was undertaken two to three decades ago through a composite

drug research program jointly conducted by the Indian Council of Medical Research and India's governmental Council for Scientific and Industrial Research (CSIR). Taking the lead from Ayurveda, a cholesterol-lowering drug, Guggulipid was developed from *Commiphora mukul*. The Drug Controller General of India approved the drug for marketing in 1986. Guggulipid is being manufactured and marketed by Cipla Ltd, Mumbai under the brand name Guglip; however, the availability of authentic raw material has remained a limiting factor. A memory enhancer derived from *Bacopa monnieri* and developed by the Central Drug Research Institute is also available in the market.(6)

Another example of the reverse pharmacology approach is a drug developed from *M. pruriens* seeds for the treatment of Parkinson's disease. A commercial product, Zandopa, manufactured by Zandu is claimed to be standardized, safe, effective, economical, and to be derived from a natural source, and which can effectively replace synthetic l-DOPA formulations in patients who comply with its dosage regimen. Regrettably, most of the efforts in reverse pharmacology approach have remained academic, and have not been pursued to any great extent in order to understand their advanced molecular mechanistics. Most likely, because of inadequate industry involvement during the development cycle, the potential of such efforts to become globally successful products was not optimally explored. The government of India's CSIR under the national network project known as the New Millennium Indian Technology Leadership Initiative (NMITLI), attempted to bridge this gap by bringing industry and academia together right from the beginning, in order to undertake herbal drug development projects on psoriasis, osteoarthritis (OA), hepatitis, and diabetes.(7)

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 cinical 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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