



REVERSE PHARMACOLOGY: A SCIENCE REDEFINING DRUG DISCOVERY

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ABSTRACT

With the increase in diversity and complexity of the diseases there is an ever-growing need of discovery and development of new drugs. Currently, the drug discovery by the conventional process is a pretty expensive and extensive process which has led to decrease in the generation of newer molecules in recent times. In view of such a situation, Reverse Pharmacology (RP) can be an effective alternative approach of drug discovery. In RP the drug discovery takes a reverse path from 'clinics to laboratory' rather than classical 'laboratory to clinics'. The already established medications in the traditional medicines are reevaluated scientifically and the lead compounds are generated which are screened further to develop a molecule which can be taken for clinical trial. RP provides an edge over the traditional drug discovery being a time saving and economical procedure. Indian Government is currently taking many initiatives to promote multidisciplinary approach for healthcare. RP has been practiced for a long time but did not get popularity because of lack of documentation and scientific standardized procedure. But, now with change in scenario and development of molecules utilizing RP, it is gaining popularity and we can hope a change in paradigm in drug discovery in future.

KEYWORDS: Reverse pharmacology; Drug discovery; Traditional medicine; New chemical entity; Pharmaceutical Industry.

INTRODUCTION

The current scenario in drug development by the pharmaceutical industry is a time consuming, complex, immensely costly and riskier process. The development of a New Chemical Entity (NCE) takes a humongous effort and letting it through the clinical development is yet again a cumbersome task.

In the recent past there has been a dip in the number of NCE being developed or an NCE getting converted into a new drug. Whereas, the cumulative cost of discovery, development and approval of a novel molecule has increased continuously without an additional advantage or development of safer and better drugs. The era of blockbuster drugs seems to wean off now and industry is more inclined towards development of me-too drugs.^[1] The pharmaceutical industry is presently seems to be under a major challenge of sustainability and growth with decreased drug discovery and increasing competition.^[2] These constraints have forced the pharmaceutical industry to end up in mergers, acquisitions or closures.^[3] However, with the increased

vigilance of regulatory agencies and authorities the classical approach of drug discovery model may no longer lead to high growth rates. The classical model of drug discovery in which the drugs (synthetic or natural) are discovered using the forward approach which involves first establishing the activity of a molecule on to the cellular or preclinical models later moving on to the clinical trial takes a pretty lengthy time and money.^[4] Natural product drug discovery, ethnopharmacology, traditional, complementary and alternative medicines are re-emerging as new strategic options in therapeutics to curb the problem of drug discovery.

In view of such obstacles in the drug discovery process we need an alternative option of drug discovery to sustain the need of ever diversifying healthcare. Reverse Pharmacology (RP) tends to be an appealing science which is rediscovering the age old used traditional medicines (TM).

Reverse Pharmacology is defined as a science of integrating documented clinical/experimental hits, into

leads by trans-disciplinary exploratory studies and further developing these into drug candidates by experimental and clinical research.^[5]

History of Reverse Pharmacology

Sir Ram Nath Chopra was a pioneer in the field of experimental pharmacology of indigenous drugs of India and is also considered as the 'Father of Indian Pharmacology'.^[6] Sir Ram Nath Chopra and Ganath Sen laid the foundation of Reverse Pharmacology of medicinal plants by pursuing clinically documented effects of Ayurvedic drugs.^[7] Sen and Kartik Bose in 1931 demonstrated the antihypertensive and tranquilizing effect of *Rauwolfia serpentina*.

Concept of Reverse Pharmacology

In RP the molecule travels a reverse path of drug discovery from 'clinics to laboratory' rather than classical 'laboratory to clinics'. In RP safety of a drug molecules stands of utmost importance and marks as a starting point whereas efficacy of the drug serves only for validation.^[8] The scope of RP is to understand the mechanisms of action at multiple levels of biological organization and to optimize safety, efficacy and acceptability of the leads in natural products, based on relevant science.^[9]

Reverse Pharmacology- The Need of the Hour

RP is designed as a science of drug development by reducing three major bottlenecks of costs, time and toxicity.^[9] With increasing diversity of diseases we need new lead and hit molecules to combat them. In low

income countries and developing countries, majority of the affected populations have little access to western medicine and they primarily depend on their traditional medicine(TM). In India, use of herbal medicines is the first line treatment in rural areas. As most of the population depends on TMs so it is better to go for the established TM system and extract the new drug molecule rather than going for conventional drug discovery to be used for primary health care.^[10]

Phases of Reverse Pharmacology^[7,8]

- 1) Experiential phase- Includes robust documentation of clinical observations of the biodynamic effects of standardized traditional drugs by meticulous record keeping.
- 2) Exploratory studies -For tolerability, drug-interactions, dose-range finding in ambulant patients of defined subsets of the disease and pre-clinical studies in relevant in vitro and in vivo models to evaluate the target-activity.
- 3) Experimental Studies-Basic and clinical, at several levels of biological organization, to identify and validate the reverse pharmacological correlates of drug safety and efficacy.

Contribution of Reverse Pharmacology to Drug Discovery

The RP has been established role in drug discovery in the past. Long time gap from the observational therapeutics to a new drug has been a major drawback. There has been a lot of discovery and some of them are summarized in the table 1.

Table 1: Summary of various established drugs from medicinal plants.^[7]

Herbal Sources	Clinical Effect	Mechanism or Site of action
Curare tomentosun	Paralysis and death	Neuromuscular block
Papaverum somniferum	Analgesia	Opioid receptors
Physostigma venenosum	Ordeal poison	Anticholinestrase
Cinchona	Fever cure	Antimalarial
Digitalis purpurea	Dropsy	Na ⁺ - K ⁺ ATPase
Salix alba	Fever and pain relief	Prostaglandins

Rauwolfia serpentina was a major discovery through RP. The antihypertensive and tranquilizing effects were discovered at the earliest and later various side effects such as depression, extra pyramidal syndrome, gynecomastia did also come into the scenario which later led to development new drugs like antidepressants, L-dopa, bromo-ergocriptine, and H₂ receptor blockers and drugs modulating prolactin.^[11,12] The drugs which were later developed are considered as a spinoff of the parent molecule. However, the extracted alkaloids from *R. serpentina* like reserpine and ajmalcine, have been used as an experimental drug in various experiments.^[13]

Withania somnifera has shown to reduce cyclophosphamide toxicity by reducing chances cyclophosphamide (CP) induced leuopenia, increasing bone marrow cellularity and also to an extent reduces the CP associated urotoxicity. On CP administration there

was a reduction in IFN-gamma, IL-2 and GM-CSF which were reversed by *Withania somnifera*.^[14,15] It has also been proved to have stress reducing property by reducing lipid peroxidation.^[16]

Psoralea corylifolia Linn has been used traditionally in the treatment of leukoderma. It has been proven to promoting skin health, hair growth, relieving attacks of asthma and bronchitis and reducing inflammatory and edematous conditions.^[7] Presently, psoralen a derivative of *Psoralea* is being used in the treatment of psoriasis along with ultraviolet light and is a proven effective therapy.^[17]

Artemisia annua is an herb which has been used for a long time in Chinese traditional medicine for malaria. Now this artemisinin and its derivatives have been successfully developed into very effective class of anti-

malarial drugs which are even effective in chloroquine resistant cases.^[18] This discovery can be considered as the best example of RP.

Picrorrhiza Kurroa has been shown to have significant hepatoprotective effect apart from having antioxidant as well as hydrocholeritic effects. It is undergoing clinical trials for the development of novel hepatoprotectives.^[19,20,21]

Curcuma longa Linn has been shown to have wound-healing, antiinflammatory and antimutagenic properties.^[22] Its property of cancer prevention has been well demonstrated in preclinical and clinical studies.^[23,24]

There is also some preclinical evidence that it can prevent the formation of plaques in Alzheimer's disease.^[25]

Commiphora Wightii is a plant which lead to discovery of Guggulu. Its hypolipidemic effects are well established and it sets a good example of RP.^[26] There is also evidence of anti-arthritic effects and of guggulu.

Table 2 summarizes the drugs which were developed as a spinoff of the incidental observation associated with the parent herbal drug. The clinical observations were finely assessed and later were used in the development of novel drugs.

Table 2: Spinoffs and serendipitous discovery.^[3,7,9,27]

Ayurvedic Plant	Evidence	Spin-Offs
Rauwolfia serpentine	Anti-hypertensive	Anti-depressants, L-dopa
Psoralea carylifolia	Anti-vitiligo	PUVA-therapy
Berberis aristata	Anti-infective	Septic shock, anti-malarial
Picrorrhiza kurroa	Anti-jaundice	Hydrocholeretic, Anti-asthma
Commiphora wightii	Anti-arthritic	Hypolipidemic
Tinospora cordifolia	Anti-pyrexial	Anti-cancer, Immune enhancer
Curcuma longa	Anti-inflammatory	Cancer-preventive
Azadirachta indica	Dermatological	Anti-cancer, anti-malarial
Terminalia chebula	Laxative	CCK-receptor, memory
Phyllanthus emblica	Anti-ageing	Free radical scavenger
Quinine	Malaria	Quinidine in Atrial fibrillation
Nitrous oxide	Laughing gas	Anaesthesia
Piperazine	Gouty tophi	Anthelmintic (Diethylcarbazine)
Aspirin	Analgesic	Anti-Platelet
Galega officinalis	Antidiabetic	Guanidines (Metformin)
Adhatoda vasica	Cough	Mucolytic (Bromhexine)
Metronidazole	Trichomoniasis	Amoebiasis (Satronidazole, Ornidazole)

Scenario of Reverse Pharmacology in India

With the recent amendment of the Drug act in India which has stressed upon inclusion of category of phytopharmaceuticals which are developed from medicinal plants with evidence of quality, safety and efficacy it is quite evident that we are now moving towards the path of RP.

The concept of RP was formally accepted by the Council for Scientific and Industrial Research (CSIR), India in view of fast track development of standardized herbal drugs. CSIR through the New Millennium Indian Technology Leadership Initiative (NMITLI) which is a national network have started various project for drug development.^[3,28] Various Randomized controlled clinical trials (RCTs) were conducted on standardized herbal formulations to prove their efficacy in diseases like diabetes, rheumatoid and osteoarthritis and hepatoprotectives. NMITLI has attempted to bring industry and academia together right from the beginning and has networked for research and development (R&D) in a multi-institutional, multi-disciplinary way. Most of these compounds are part of routinely used traditional medicines and hence their tolerance and safety is

assumed to be better than any other chemical entities that are totally new for human use. Advanced Centre for Reverse Pharmacology has been established by Indian Council of Medical Research (ICMR) in collaboration with the Centre of Molecular Parasitology at the Drexel University College of Medicine, where the focus is on diabetes, musculo-skeletal disorders, malaria, cancer and neurological disorders.^[3]

Department of Science & Technology (DST), Govt. of India (GOI) started a project for the R&D of herbal vaccine adjuvant, which was taken by the Interdisciplinary School of Health Sciences, University of Pune with Serum Institute of India.^[29] In a very less time period they have identified semi-pure leads with substantial efficacy and also have developed toxoid and recombinant vaccines.^[29,30] Similar a nationwide project for osteoarthritis is also being run under NMITLI project which involves a network of 16 national research institutions, tertiary advanced hospitals and pharmaceutical industries from India.^[31,32,33]

Guggulipid was developed from Commiphora mukul with a composite drug research program jointly

conducted by ICMR and CSIR of GOI. DCGI approved the drug for marketing in 1986 and presently being manufactured and marketed by Cipla (Guglip). Bacopa monnieri extract was developed as a memory enhancer by CDRI, Lucknow and now is available commercially.^[8]

Hurdles in the Path of Reverse Pharmacology

- Despite a vast potential and possibilities there are a very few success stories which can be attributed to the long-time lag from the observational therapeutics converting into a new drug.
- Most of the work in this field has remained within clinics of traditional practitioners or confined to academic research laboratories
- Used for ages but lack of documentation of the traditional medicine makes it inferior to evidence based western medicine.
- Lack of proper identity, implementation of Good Laboratory Practices and Good manufacturing practices
- Lack of political and financial support
- Cultural prejudice for alien science
- There is a major impact of scientific or technical contributions from the pharmaceutical companies without which the drug discovery tends to run at a very slow pace.

CONCLUSION

At presently, global pharmaceutical industry is looking for novel and innovative solutions to curb the invention deficit to re-activate and rejuvenate the drug discovery pipeline. With such an overview, India and its diverse and pluralistic health care system offers immense potential for natural product drug discovery and development based on traditional knowledge and clinical observations. Awareness of the value of traditional medicine should be focused on. It is essential to create an academic environment and awareness of RP in medical and pharmaceutical colleges which would plant the idea right from the beginning. A constant financial and system support is expected from the government which has been provided by the GOI which would help the NMITLI project to reach to its excellency.

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