AYURVEDA AND REVERSE PHARMACOLOGY: AN APPROACH FOR DRUG DISCOVERY

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Summary

Reverse pharmacology is the science of integrating documented clinical experiences and experimental observations into leads by interdisciplinary exploratory studies and further developing these into drug candidate or formulations through robust preclinical and clinical research. It mainly relates to reversing the routine laboratory to clinic progress of discovery pipeline to clinic to laboratories. In this safety are the most important starting point and efficacy remains a matter of validations. Found to be a tool for new drug discovery in conjugation with herbal drugs specifically those which are official in ayurvedic formularies. With recent advances in drug discovery it is proved to be an excellent and efficient method one can adopt to search newer entities with potential pharmacological activities in future.

Key-words: Ayurveda, Drug Discovery, Ethamopharmacology, Reverse Pharmacology.

Introduction

The ayurvedic knowledge database allows drug researchers to start from a well-tested and safe botanical material. With ayurveda, the normal drug discovery course of 'laboratories to clinics' actually becomes from 'clinics to laboratories' – a reverse pharmacology approach. In this process safety remains the most important starting point and efficacy becomes a matter of validation. Globally, there is a positive trend towards holistic health, integrative sciences, systems biology approaches in drug discovery and therapeutics that has remained one of the unique features of ayurveda.[1] A golden triangle consisting of ayurveda, modern medicine and science will converge to form a real discovery engine that can result in newer, safer, cheaper and effective therapies. It will be in the interest of pharmaceutical companies, researchers and ultimately the global community to respect the traditions and build on their knowledge and experiential wisdom.

Reverse pharmacology is defined as the science of integrating documented clinical experiences and experimental observations into leads by interdisciplinary exploratory studies and further developing these into drug candidate or formulations through robust preclinical and clinical research. It mainly relates to reversing the routine laboratory to clinic progress of discovery pipeline to clinic to laboratories. In this safety is the most important starting point and efficacy remains a matter of validation. [2]

Sir Ram Nath Chopra and Gananath sen laid the foundation of reverse pharmacology of ayurvedic drugs. Sen and Bose in 1931 demonstrate the antihypertensive and tranquilizing effect of *Rawolfia serpentina* and also observed unique side effects such as depression, extra pyramidal syndrome, gynecomastia and peptic ulcer. This will lead to development of newer antidepressant and ant Parkinson's drugs. Post-genomic advances in bioinformatics have fostered the development of rational drug-design strategies that seek to reduce serious side-effects. This era has brought about the concept of *reverse pharmacology*, in which, the first step is the identification of protein targets, that may be critical intervention points in a disease process.[3] Since this method is driven by the mechanics of the disease, it is expected to be more efficient than the classical approach. Rapid identification of enzyme (or protein) targets needs a thorough understanding of the underlying metabolic network of the organism affected by a disease. The availability of fully sequenced genomes has enabled researchers to integrate the available genomic information to reconstruct and study metabolic networks. These studies have revealed important properties of metabolic networks. The potential of an enzyme to be an effective drug target is considered to be related to its essentiality in the corresponding metabolic network. Lemke et. al proposed the measure *enzyme damage* as an indicator of enzyme essentiality.[4] Recently, a computational approach to prioritize potential drug targets for antimalarial drugs was developed . A choke-point analysis of *P.falciparcum* was performed to identify essential enzymes which are potential drug targets. The possibility of using enzyme inhibitors as antiparasitic drugs is being investigated through stoicheometric analysis of the metabolic networks of parasites. These studies show the effectiveness of computational techniques in reverse pharmacology. The basis of traditional medicine is in its use for a number of years and therefore its clinical existence comes as a presumption. However, for bringing more objectivity and also to confirm traditional claims, systematic clinical trials are necessary. In ayurvedic medicine research, clinical experiences, observations or available data becomes a starting point. In conventional drug research, it comes at the end. Thus, the drug discovery based on ayurveda follows a 'reverse pharmacology' path.[5]

Nevertheless; all the critical pharmacopoeial tests such as dissolution time, microbial, pesticide and heavy metals contamination, etc. must be in accordance with global standards. It is important to ensure that all the ayurvedic medicine manufacture is in accordance with current good manufacturing procedures for herbal products.[6] There have been concerns about quality standards and safety issues of herbal medicines. The need for new regulations for botanical medicines has also been frequently stressed and some such regulations are coming into force in different parts of the world.[7]

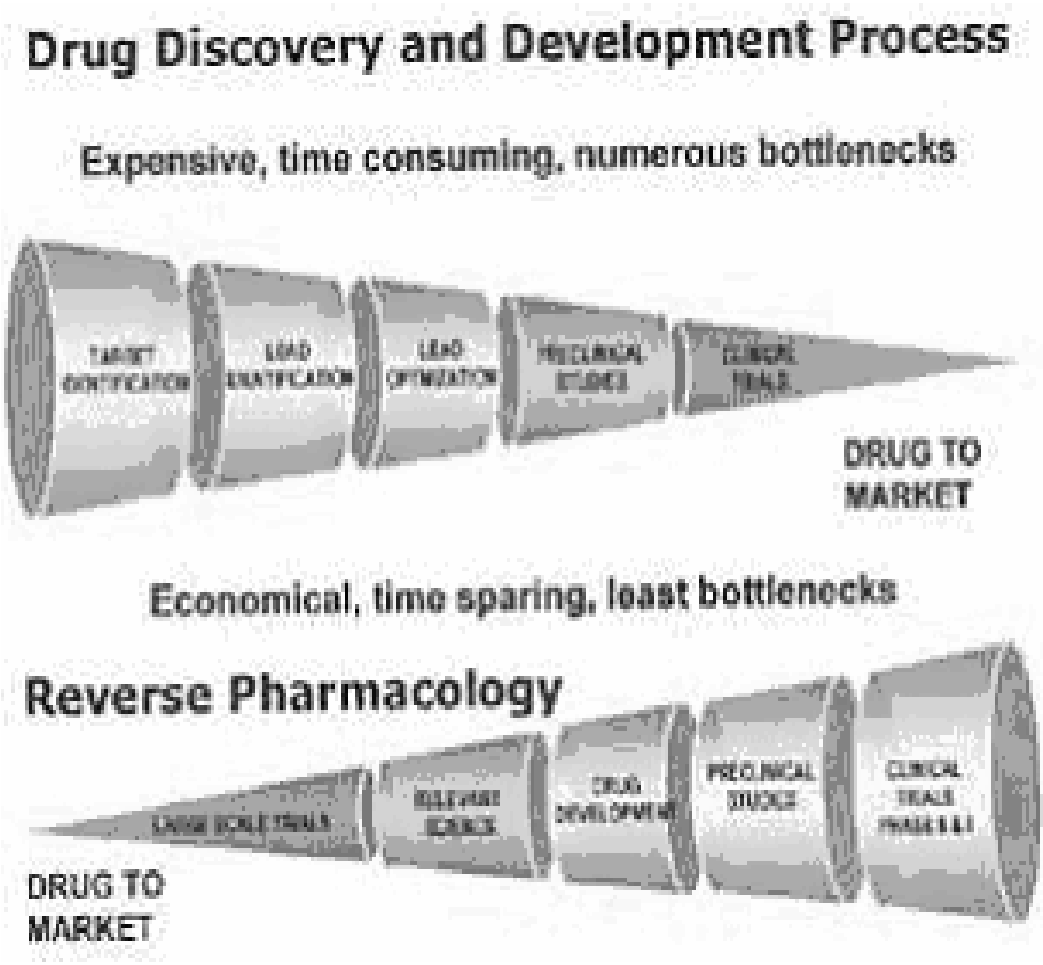

Fig: 1: Drug discovery and Development process

Reverse pharmacology helps in reducing three major bottlenecks costs, time and toxicity.

Orphan GPCRs

Even though GPCRs have been intensely investigated as potential drug targets, their structural and functional diversity [8], still offer opportunities to develop novel drugs. The analyses of the human genomic sequence suggest that there may be 750 human GPCR encoding genes, of which approximately 160 cannot be functionally characterized either on the basis of sequence homology or by association with known endogenous ligands. These are referred to as orphan GPCRs (GPCRs) which bind (as yet) unknown ligands.[9] G protein-coupled receptors (GPCRs), also known as seven-transmembrane domain receptors, 7TM receptors, heptahelical receptors,

serpentine receptor, and G protein-linked receptors (GPLR), comprise a large protein family of transmembrane receptors that sense molecules outside the cell and activate inside signal transduction pathways and, ultimately, cellular responses. G protein-coupled receptors are found only in eukaryotes, including yeast, choanoflagellates and animals. Reverse pharmacology is an approach that can be used for GPCRs deorphanization. Based on the idea that GPCRs are targets of neurotransmitters, peptides, hormones and other transmitters, it can be expected that orphan GPCRs are also activated by transmitter molecules. Then the orphan GPCR is used as a target to test potential transmitters.[10] The first efforts to identify ligands for orphan GPCRs began in the mid-1980s. At that time, the number of known potential transmitters was large. This became reverse pharmacology in an important approach to this aim. The first successful deorphanization of orphan GPCRs were reported in 1988. HT1A receptors and dopamine D2 receptors. The strategies used were the same, that is, the orphan GPCR was expressed by DNA transfection in eukaryotic cells, membranes of these cells were then used as targets to determine the binding of potential transmitters. Since early 1990s, the application of the reverse pharmacology strategy led to the pharmacological characterization of much GPCRs. Reverse pharmacology has been adapted to allow for the screening of a large battery of potential transmitters on batteries of orphan GPCRs by using high throughput screening techniques. This has made it possible to match several dozens of orphan GPCRs to their ligands. But all these ligands had been previously discovered and there was a need to identify new transmitters. While over the years, numerous orphan GPCRs have been matched to specific ligands, there are over one hundred GPCRs that do not bind any known transmitters.[11] In the mid-1990's a parallel approach was devised to use orphan GPCRs as targets to find novel, still non-described transmitters. This has been termed the "orphan receptor strategy". The method consists of expressing an orphan GPCR by transfection into eucaryotic cell lines, preparing a tissue extract expected to contain the transmitter specific to the orphan receptor and monitoring the activation of the GPCR by applying finely fractioned tissue extract over these engineered cell lines. The activation of the orphan GPCR is monitored by measuring second messenger responses. Positive extracts are fractionated biochemically until the active component is isolated and characterized. This approach has led to the discovery of dozens of bioactive peptides. The orphan receptor strategy was first applied in 1995 to the discovery of a novel neuropeptide called orphanin FQ or nociceptin (or OFQ/N). Traditionally the existence of a transmitter was postulated on the basis of a particular physiological response and was isolated using that response as an assay. The orphan receptor strategy reverses this approach and allows the isolation of transmitters with unknown physiology and linkage to a disease process. The success of this approach, however, is a big leap towards understanding the transmitter system by using the receptor as a vehicle to unravel its physiological function.[12]

Table no: 1 Some ligand-orphan GPCR pairings identified using reverse pharmacology strategy

Receptor	Ligand	Physiological function	References
Adenosine A1, A2A (RDC7,RDC8)	Adenosine	Platelet function, anxiety	13
ORL-1	Nociceptin/Orphanin FQ	Stress, pain	14

Orexin-1 and 2	Orexins/Hypocretins	Food intake, sleep wakefulness	15
GPR10	Prolactin-releasing pe ptide	Sleep, absence seizure	16
APJ	Apelin	Unknown	17
GHS-R	Ghrelin	Food intake, GH sec ret ion	18
SLC-1(MHC1)	MCH	Food intake	19
GPR14	Urotensin II	Vasoconstriction	20
Histamine H3 (GPCR97)	Histamine	Central nervous system obesity, psychiatry	21
FM-3/4	Neuromedin U	Unknown	22
Histamine H4 GPRv53	Histamine	Inflammation, eosinophil Chemotaxis	23

Table no 2: Drugs obtained by the reverse pharmacology path

Sr.no	Medicinal Plant	Disease
1	Rauwolfia serpentina	Hypertension
2	Commiphora wightii	Hyperlipidaemia
3	Mucuna pruriens	Parkinson disease
4	Picrorrhiza kurroa	Hepatitis
5	Curcuma longa	Oral cancer
6	Catharanthus roseus	Cancer
7	Cinchona officinalis	Malaria
8	Digitalis purpurea	Heart Failure
9	Salix alba	Fever
10	Ephedra sinensis	Asthma

Conclusion

The concept of research is directed to search for the new chemical entities for the treatment of life threatening diseases. The current review is an attempt made to utilize the principles of reverse pharmacology in conjugation with Ayurveda to develop newer strategies for the drug discovery which will offer newer chemical entities with potential biological activities.

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