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Reverse pharmacology "A new outlook in the drug development process"

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ABSTRACT

The pharmaceutical industry has historically seen an Incredible growth primarily due to the discovery of blockbuster drugs with the potential to generate over 1 billion US $ sales , however recent trends indicate that this model may no longer lead to high growth rates . The industry is really facing a major challenge to sustain and grow. Drug discovery and development process involves a 10- 15 years of investigation period and investments between US $1 billion and $ 1.5 billion. This resulted in "Target Rich Lead Poor" performance. The world health organisation's commission on Intellectual property and Innovation in public health has also duly recognised the promise and role of traditional medicine in drug development for affordable health solutions .In this scenario Reverse pharmacology plays a vital role and can be defined as the integrating science of developing candidate drugs from a clinical to experiential hits and leads by transdisciplinary exploratory studies to understand the mechanisms of action at different pathological stages of biological organism . Then, confirm candidate drugs from experimental to clinical use on the basis of safety, efficacy and acceptability on relevant science potentiating fast track drug discovery and development of safer and effective drugs. India being a pluralistic health care system offers immense opportunities for natural product drug discovery and development based on traditional knowledge and clinical observations.

Keywords: Reverse pharmacology, Pharmacoepidemiology, Mucuna pruriens, Argemone Mexicana, l-dopa.

INTRODUCTION

Reverse pharmacology is the science of integrating bedside documented experiential hits into leads by transdisciplinary exploratory studies (in vitro and in vivo) and to further develop the leads into drug candidates by state of the art experimental and clinical research. Gananath sen laid the foundation for reverse pharmacology of ayurvedic drugs, hence Gananath sen is considered as the father of reverse pharmacology [1]. According to sir Austin Bradford hill, the pioneer of medical statistics and clinical drug trials, all scientific work is incomplete whether it be observational or experimental .The scientific work is liable to be upset or modified by advancing knowledge. It is the emphasis on not to ignore the knowledge we already have. Ayurveda, in India is used from centuries for treatment of various chronic diseases .The natural products of ayurveda have a vast potential for novel phyto molecules with clinical activity. Reverse pharmacology in a broader sense means to pursue bedside observations back to the laboratory bench for new drugs.

Drug discovery: current scenario

Drug discovery and development process involves a 10- 15 years of investigation period and investments between US $1 billion and $ 1.5 billion. This resulted in "Target Rich Lead Poor" performance. The world

health organisation's commission on Intellectual property and Innovation in public health has also duly recognised the promise and role of traditional medicine in drug development for affordable health solutions**.** [2]

Scope of reverse pharmacology

The scope of reverse pharmacology is to understand the mechanisms of action at multiple levels of biological organisation and to optimize safety, efficacy and acceptability of the leads from natural products based on relevant science. The phytoactive constituents can serve as chemical scaffolds for novel medicinal chemistry.[3] These are the major domains of reverse pharmacology.

The Experiential Domain

It covers the literature Search and pharmaco epidemiology aspects.

The Exploratory Animal Studies

It covers in vitro and In vivo studies, human pharmacology and phase 2 Studies for dose finding.

The Experimental Domain and Clinical Investigation

It covers efficacy and safety issues.

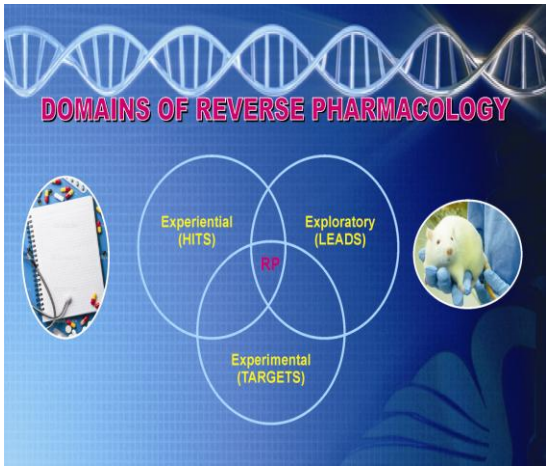

Figure A: Domains of Reverse Pharmacology

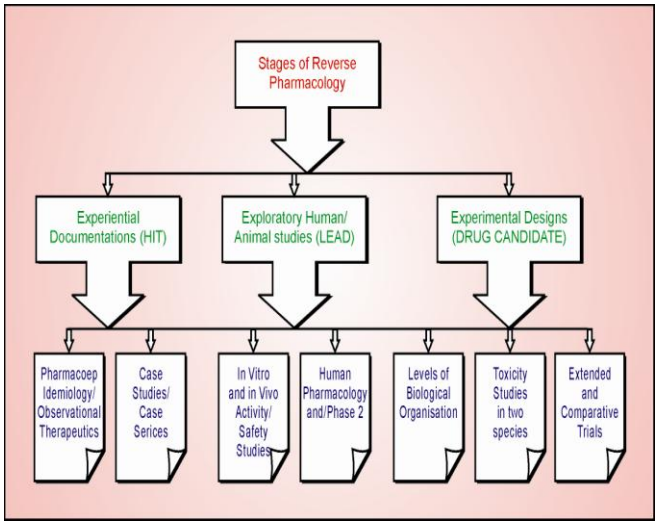

Figure B: Stages of Reverse Pharmacology

RECENT DEVELOPMENT

Anti-malarial

The discovery of Artemisinin for malaria is a result of scientific work based knowledge from Traditional Chinese medicine (TCM) and presents best case for reverse pharmacology approach. Artemisia annua has been used for many centuries in Chinese traditional medicine as a treatment for malaria.

Anti-parkinson's

Ayurvedic physicians in ancient India first used mucuna pruriens seeds for the treatment of Parkinson's disease. The dose used by ayurvedic physicians is small as compared to synthetic l-dopa (laevorotatory form of dopa). These observations inspired scientists to further study and led to collaboration between academia and zandu pharmaceuticals from Mumbai. This team conducted series of experiments on mucuna to develop a natural drug for Parkinson's disease. The USFDA (United States Food and Drug Administration) has approved NDA (New Drug Application) for clinical studies. Zandopa is now approved by the Indian FDA (Food and Drug Administration). This standardised, safe and economical natural product can effectively replace synthetic l-dopa formulations. [4]

Anti-hypertensive

The best example of bio-prospecting using traditional knowledge is Reserpine, the anti-hypertensive alkaloid from rauwolfia serpentina [5], which became available as a result of work carried out by CIBA pharmaceuticals in India in close collaboration with ayurveda experts.

Superliner

The normal drug discovery course of "Laboratory to clinics" in this case actually becomes "Clinics to laboratories."[**6**]

CASE STUDY: REVERSE PHARMACOLOGY

Argemone Mexicana

A Reverse pharmacology approach is presented for the treatment of uncomplicated malaria. In natural products research , compounds are generally tested in vivo only after full in vitro characterisation, however drug screening using this methodology is expensive , time consuming and very often inefficient . So reverse pharmacology also called bedside to bench is a research approach based on the traditional knowledge and relates to reversing the classical "laboratory to clinic pathway" to a "clinic to laboratory practice". In this case study, reverse pharmacology approach was applied to the decoction of Argemone Mexicana, used as an anti-malarial traditional medicine in Mali. Argemone Mexicana appeared as the most effective traditional medicine for the treatment of uncomplicated falciparum malaria in Mali and the clinical efficacy of the decoction was comparable to artesunate. [7]

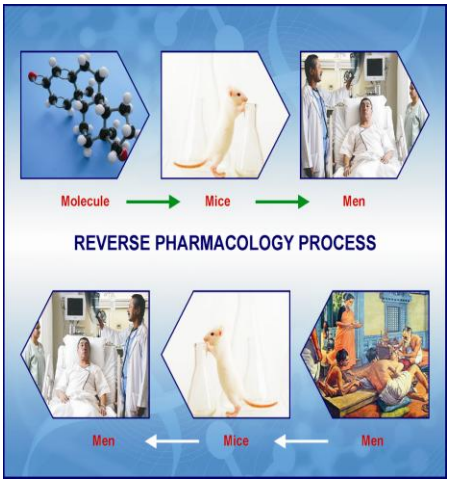

Figure C: Reverse Pharmacology Process

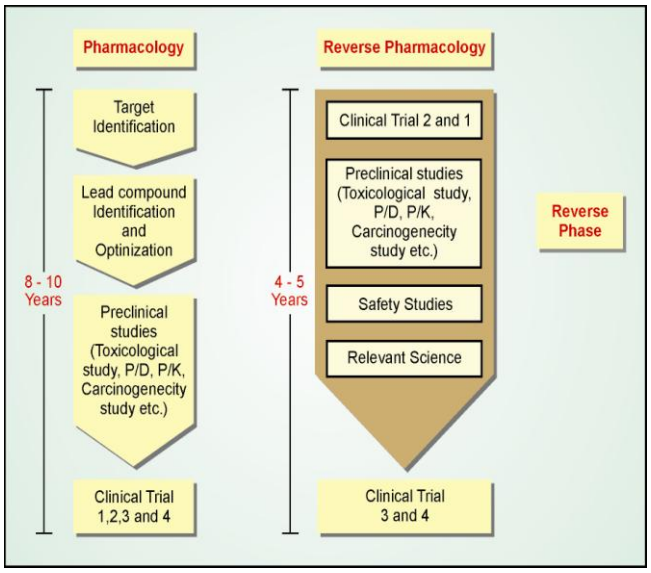

Figure D: Comparative Flow Diagram of Pharamacological Research and the Reverse Pharamacology Research

CONCLUSION

The three main bottlenecks in drug development (time, money, and toxicity) can be easily addressed by Reverse pharmacology. It potentiates fast track drug discovery and development of newer, safer and effective drugs. India being a pluralistic health care system offers immense opportunities for natural product drug discovery and development based on traditional knowledge and clinical observations, with Ayurveda, the normal drug discovery course of "laboratory to clinics" actually becomes "clinics to laboratories". So it can be concluded that reverse pharmacology research starts almost where pharmacology ends i.e. to find drugs or herbal products in current use with collateral effects and take them back into the lab and conduct trial for any other new indications.

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