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REVERSE PHARMACOLOGY AND SYSTEMS APPROACHES FOR DRUG DISCOVERY AND DEVELOPMENT

***KRISHNA P., T .MERCY MARGARET, B.REVATHI, B.BRAHMAIAH, SREEKANTH NAMA, PRASANNA KUMAR DESU.**

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Priyadarshini Institute of Pharmaceutical Education and Research, 5th Mile, Pulladigunta, kornepadu (M), Guntur (DT), A.P, India.

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Corresponding Author

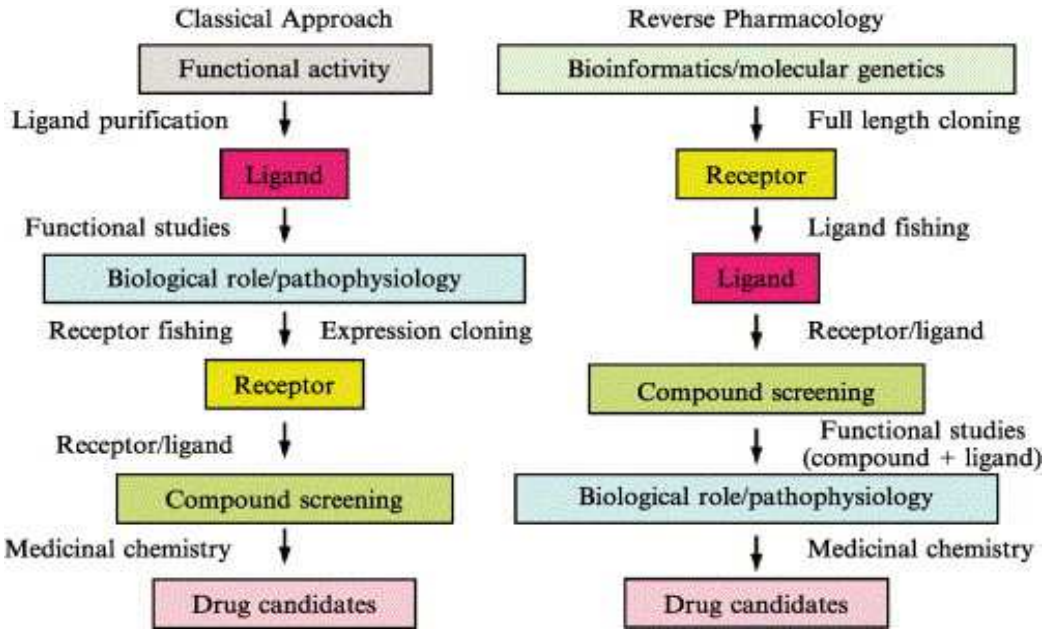
Mr. Krishna P

Abstract

Scientifically validated and technologically standardized botanical products may be explored on a fast track using innovative approaches like reverse pharmacology and systems biology, which are based on traditional medicine knowledge. Traditional medicine constitutes an evolutionary process as communities and individuals continue to discover practices transforming techniques. Many modern drugs have origin in ethno pharmacology and traditional medicine. Traditions are dynamic and not static entities of unchanging knowledge. Discovering reliable 'living tradition' remains a major challenge in traditional medicine. In many parts 'little traditions' of indigenous systems of medicine are disappearing, yet their role in bio prospecting medicines or poisons remains of pivotal importance. Indian Ayurvedic and traditional Chinese systems are living 'great traditions'. Ayurvedic knowledge and experiential database can provide new functional leads to reduce time, money and toxicity - the three main hurdles in the drug development. We begin the search based on Ayurvedic medicine research, clinical experiences, observations or available data on actual use in patients as a starting point. We use principles of systems biology where holistic yet rational analysis is done to address multiple therapeutic requirements. Since safety of the materials is already established from traditional use track record, we undertake pharmaceutical development, safety validation and pharmacodynamic studies in parallel to controlled clinical studies. Thus, drug discovery based on Ayurveda follows a 'Reverse Pharmacology' path from Clinics to Laboratories. Herein we describe such approaches with selected examples based on previous studies.

INTRODUCTION:

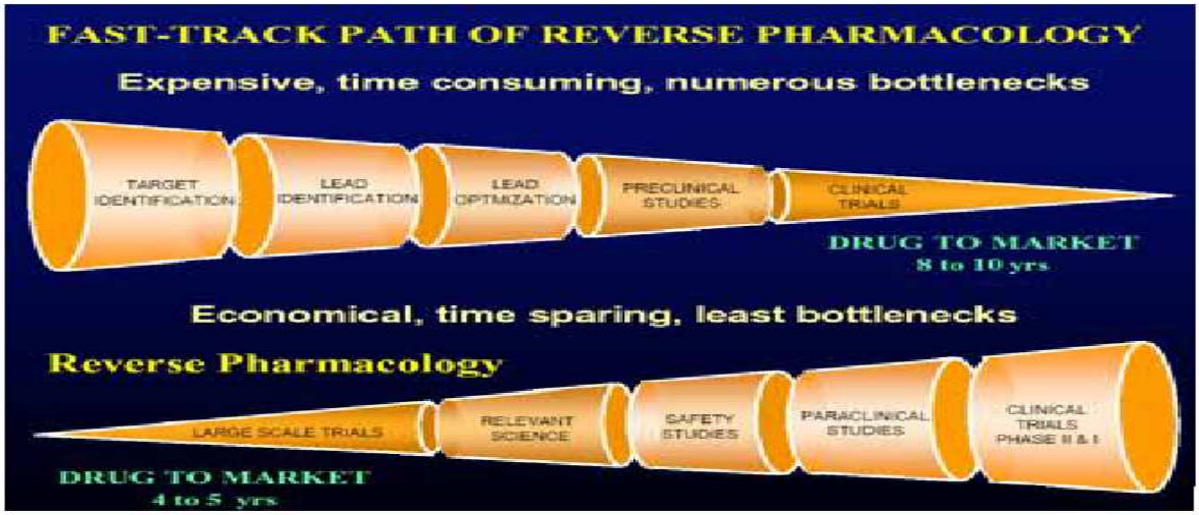
The pharmaceutical sector has traditionally been a vibrant, innovation-driven and highly successful component of global industry [1]. A confluence of spectacular advances in chemistry, molecular biology, genomics and chemical technology and the cognate fields of spectroscopy, chromatography and crystallography led to the discovery and development of numerous novel therapeutic agents for the treatment of a wide spectrum of diseases. To facilitate this process, scientists launched a significant and noticeable effort aimed at improving the integration of discovery technologies, chemical sourcing for route selection / delivery of active pharmaceutical ingredients. Drug discovery and development was increasingly done sans frontiers with collaborations spanning the globe and utilizing scientists with a broad array of technical, professional and cultural boundaries [2, 3].



REVERSE PHARMACOLOGY (RP)

Sir Peter B. Medawar rightly stated that "A synthetic discovery is always a first recognition of an event, a phenomenon, process, or a state of affairs not previously recognized or known. Most of the stirring and deeply influential discoveries of science

come under this heading" [4]. Clinical events or phenomena previously not reported and following the administration of a known or new drug, can provide valuable insights for drug development. Medicinal plants and natural products derived there from have provided many such serendipitous bedside observations. Historically, several such clinical hits were not often pursued quickly and rigorously by the drug discovery teams. A new trans-disciplinary endeavor called Reverse Pharmacology has recently emerged and addresses both these needs. Reverse Pharmacology (RP), designed as an academic discipline to reduce three major bottlenecks of costs, time and toxicity [5, 6].



REVERSE PHARMACOLOGY FOR MODERN DRUGS:

Reverse Pharmacology as a term has two nuances. The first is the path of pharmacology from the bedside observation to bench experiments. The second is the search of drug-like molecules (endogenous or extrinsic) which dock-in with new macromolecules discovered through genomics and proteomics [7, 8].

For the present discussion, we will focus on the first meaning of Reverse Pharmacology. Reverse Pharmacology is a trans discipline that is comprised of three stages [9, 10]:

1) Experiential hits-documentation in observational Therapeutics and Pharmaco epidemiology.

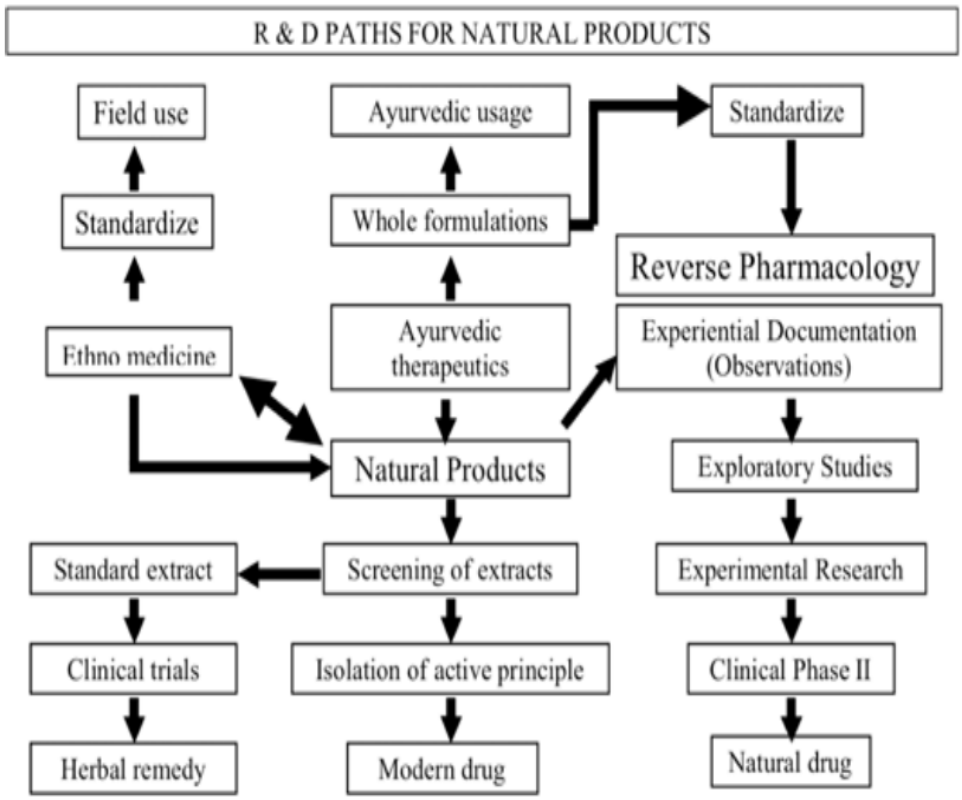
2) Exploratory stage of in vitro and in vivo studies to develop these hits.

3) Experimental and clinical state-of-the-art relevant scientific research to determine safety, efficacy and mechanisms of action of the candidate drug. The scope of Reverse Pharmacology.

REVERSE PHARMACOLOGY FOR NATURAL PRODUCTS:

Multiple cell types and diverse pathways contribute to the disease, a single molecule may not be effective in modulation of multiple targets and such conditions require combination therapy. witnessing the entry of a new informational paradigm into medicine that is most prominently represented by proteomics, metabolomics sciences. Metabolomics is a systems approach for studying metabolic profiles, which promises to provide information on drug toxicity, disease processes and gene function at several stages in the discovery process [11].

Reverse Pharmacology and Systems Approaches for Drug Discovery *Current Bioactive Compounds* 2008, *Vol. 4,*



REVERSE PHARMACOLOGY CORRELATIONS:

Table 1. Reverse Pharmacology Correlates

Diabetes mellitus	Osteoarthritis	Hepatitis
• GLUT-4 translocation	• Chondrocyte protection	• Hepatoprotective- Anti TB drugs
• AKT-phosphorylation	• Disease-modifying	• Proinflammatory cytokines decrease
• Inhibition of glycation	• Muscular Strength	• Protection- Paracetamol
• Cataract prevention	• MRI improvement	• Reduction in fatty infiltration

Reverse Pharmacology: a strategy for new drug discovery

For the last three decades our research group, firstly at CIBA Research Centre and Podar Hospital and later at SPARC and MRC-KHS, has been engaged in evolving Reverse Pharmacology as a novel strategy for new drug discovery. This was followed up by CSIR-NIMITLI projects for diabetes mellitus, arthritis, hepatitis and psoriasis. ICMR has granted the first Advanced Centre in Reverse Pharmacology to our Kasturba Health Society. The CSIRNMITLI programme was quite successful.32 Several hits, leads and drug candidates have evolved over the last seven years. However, the pharmaceutical industry is still lukewarm in taking up this new paradigm for drug discovery [12].

A "reverse pharmacology" approach to developing an anti-malarial phytomedicine:

A "reverse pharmacology" approach to developing an anti-malarial phytomedicine was designed and implemented and resulting in a new standardized herbal anti-malarial after six years of research. The first step was to select a remedy for development, through a retrospective treatment-outcome study. The second step was a dose escalating clinical trial that showed a dose-response phenomenon and helped select the safest and most efficacious dose. The third step was a randomized controlled trial to compare the phytomedicine to the standard first-line treatment. Malaria elimination efforts will lead to the much wider use of the few currently effective anti-malarial drugs, such as artesunate / amodiaquine, artesunate / sulphadoxinepyrimethamine (SP), and artemether / lumefantrine. There is already discussion about intermittent presumptive treatment of infants, children, pregnant women, and even mass drug administration in some settings [1]. Resistance already exists to amodiaquine and SP, and will probably increase as a result of the increased drug pressure. Traditional medicinal plants have provided the source of the two major families of anti-malarial drugs still in use today, artemisinin and quinine [13].

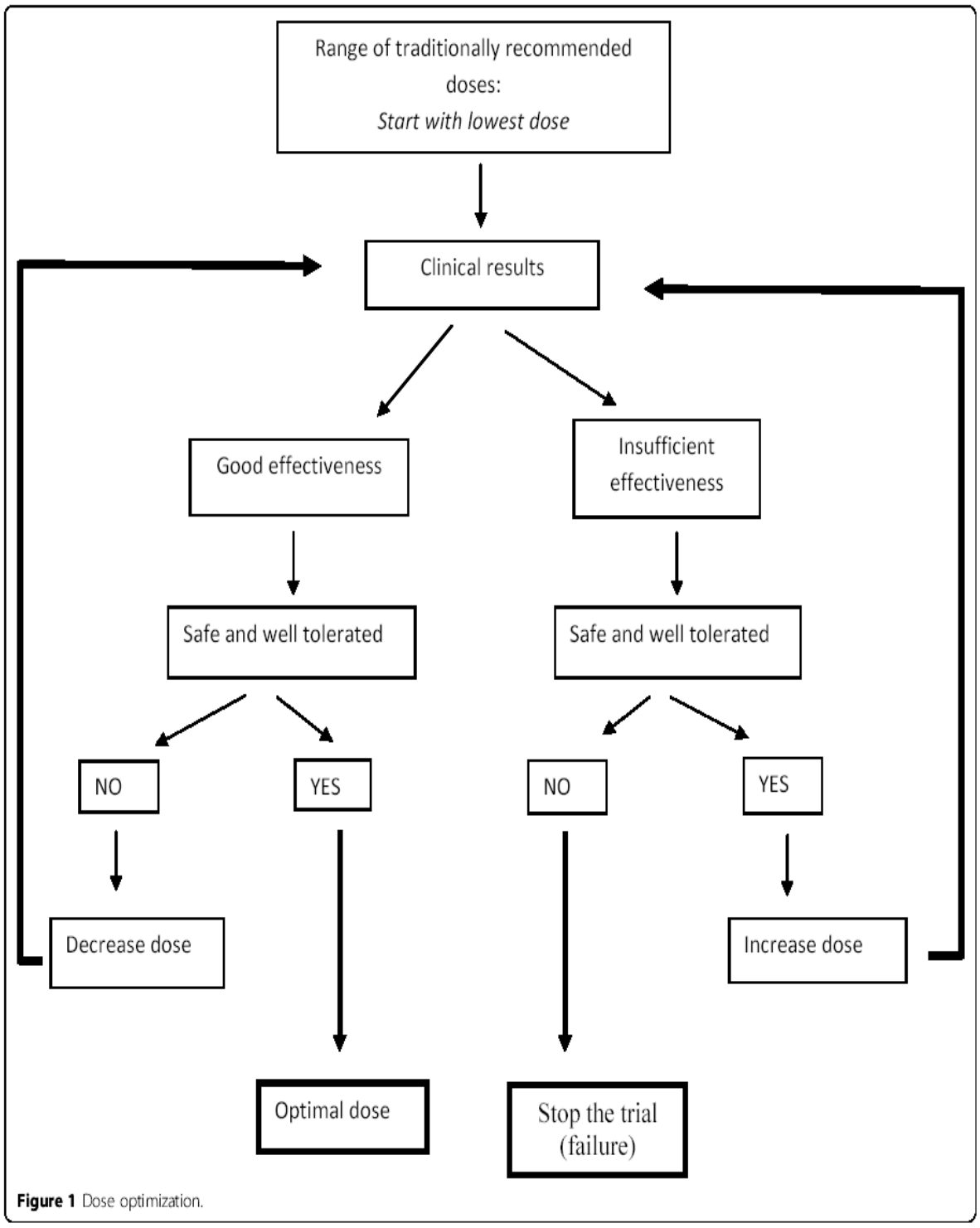


Figure 1 Dose optimization.

THE METHODS USED TO DEVELOP ANTI MALARIAL PHYTOMEDICINE BY REVERSE PHARMACOLOGY:

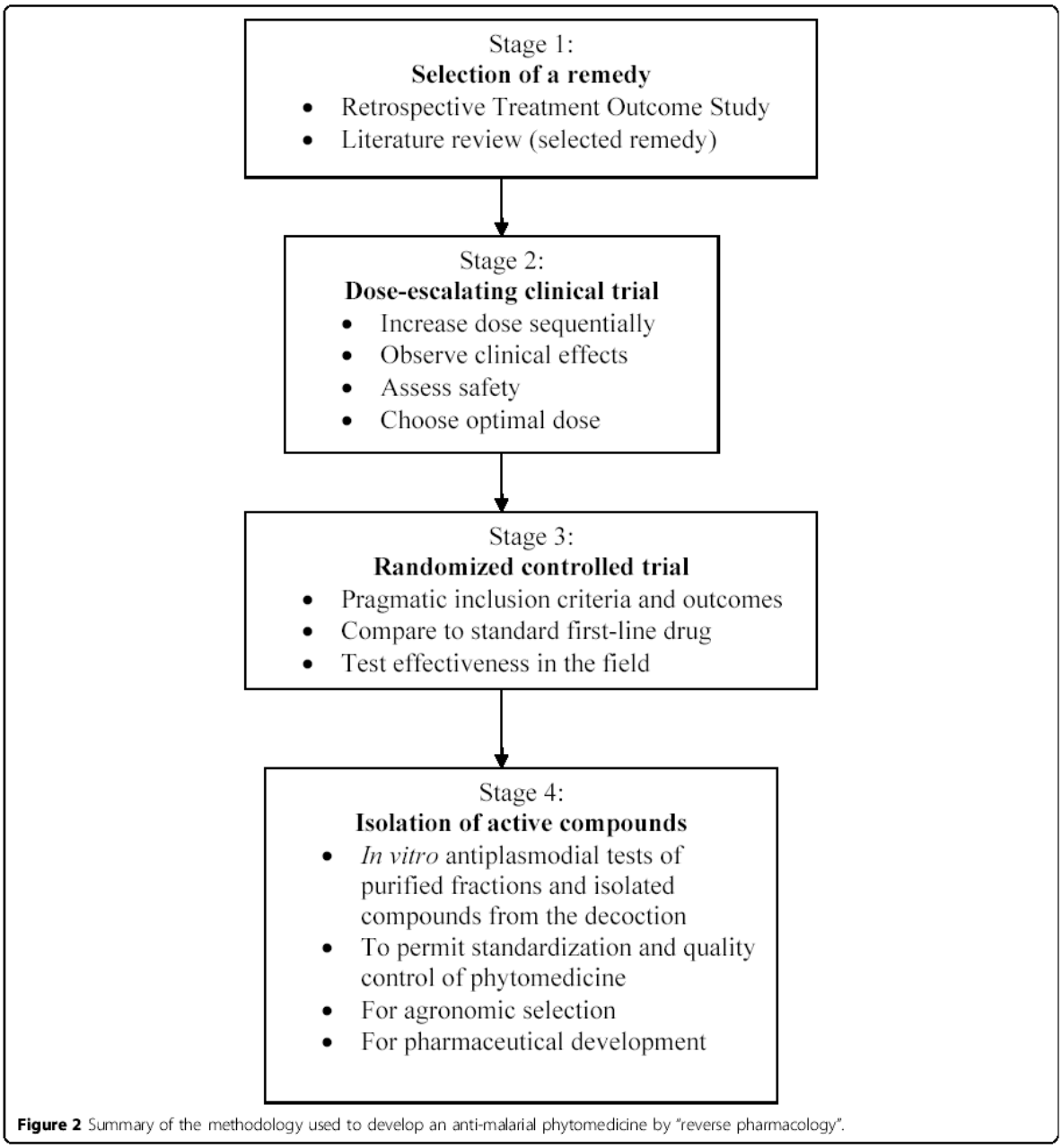


Figure 2 Summary of the methodology used to develop an anti-malarial phytomedicine by "reverse pharmacology".

REVERSE PHARMACOLOGY STRATEGY:

Table 2. Some ligand-orphan GPCR pairings identified using reverse pharmacology strategy

Receptor	Ligand	Year	Major function	Refs
Adenosine A_1, A_{2A} (RDC7,RDC8)	Adenosine	1990-1991	Platelet function, anxiety	[82,83]
ORL-1	Nociceptin/Orphanin FQ	1995	Stress, pain	[94]
Orexin-1 and 2	Orexins/Hypocretins	1998	Food intake, sleep-wakefulness	[95, 96]
GPR10	Prolactin-releasing peptide	1998	Sleep, absence seizure	[97]
APJ	Apelin	1998	Unknown	[98]
GHS-R	Ghrelin	1999	Food intake, GH secretion	[99, 100]
SLC-1(MHC1)	MCH	1999	Food intake	[101, 102]
GPR14	Urotensin II	1999	Vasoconstriction	[103]
Histamine H3 (GPCR97)	Histamine	1999	Central nervous system-obesity, psychiatry	[88]
FM-3/4	Neuromedin U	2000	Unknown	[104, 105]
Histamine H4 GPRv53	Histamine	2000	Inflammation, eosinophil chemotaxis	[89]
GPR54	Mestatin	2001	Cell proliferation, development	[106, 107]
GPR73 a/b	Prokineticin ½	2002	Angiogenesis, circadian rhythm	[108, 109]
GPR7 and GPR8	NPB and NPW	2002	Food intake, unknown	[110, 111]
GPCR135 and GPCR142	Relaxin	2003	Unknown	[112, 113]
GPR91	Succinate	2004	Increases blood pressure	[114]

Conclusion: 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 Surh / Journal of Traditional and Complementary Medicine 1 (2011) 5-7 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 clinical 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.

ACKNOWLEDGEMENTS

Although, Reverse pharmacology as a concept was proposed and mainly promoted by one of us (ADBV), it draws inspiration from several researchers who have contributed to evidence based studies on Ayurveda and traditional medicine. We have cited few such scientists and representative case studies, however, there many such who may not have appeared in this article due to limitations on space, we wish to gratefully acknowledge all of them and the great wisdom of several unsung Ayurvedic vaidyas from whom we have

received inspirations. We also thank CSIR NMITLI program for formally adopting RP as a strategy for fast track drug discovery and development.

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