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Reverse Pharmacological Approach: A Narrative Review

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Abstract:

The situation of drug research and development today is unsurmountable, notwithstanding notable advancements in high throughput tests. New approaches to medication research are therefore desperately needed. Almost 70% of Indians used Ayurveda. It is time to change the way that native plants are systematically and empirically searched for their potential health benefits. Reverse pharmacological techniques, observational studies, and Ayurvedic epidemiology have yielded impressive results, indicators, as well as parts for a variety of illnesses and ailments. Potential frameworks to medicinal chemists to increase efficacy while reducing toxicity will include the possible phyto base entity. Numerous indigenous medicinal herbs have demonstrated efficacy. Reverse pharmacology uses conventional drugs with a track record of therapeutic action as a springboard for new drug discovery. On the other hand, known natural product medications from conventional medicine are typically blends of substances with various pharmacological effects. Because of the intricate interplay between the components' pharmacological effects and the traditional drug's overall pharmacological effects, it is very challenging to determine which of its active ingredients they are and to understand their mechanisms of action. The main concept utilised to solve this issue is that approaches to drug development that are influenced by traditional medicine should begin with the significance of determining the content foundation for the effectiveness and elucidating the way that pharmacology works in conventional drugs. Many organisations employ reverse pharmacology worldwide to create new compounds, formulations, and baits for drugs.

Key words- Efficacy, Safety, Traditional Medicine, Methodology; reverse pharmacology

1. INTRODUCTION

Reverse pharmacology uses conventional drugs with a track record of therapeutic action as a springboard for new drug discovery. (1) A fundamental idea behind the reverse pharmacology methodology was put forth: using the traditional drug's pharmacological effect as a point of citation, the consequences individual elements and/or component combinations were contrasted to the conventional medication in order to identify a lead compound or mixture that could generate the original drug's medicinal impact.(2) It is now imperative to change the way these native plants are thoroughly and scientifically investigated to find any potential health benefits. In order to provide this clarity, numerous new scenarios and methods were created. Reverse pharmacological techniques, observational research, and Ayurvedic epidemiology have yielded impressive results..(3)

Millions of compounds have been synthesised by chemists for use in drug screening studies, however it is challenging to find and create novel drugs using the libraries of compounds that are now available. However, when a new drug from traditional medicine is researched and developed using the reverse pharmacology research framework, the time and cost can be significantly decreased.(4) The medication is utilised in reverse pharmacology and is currently in clinical use. Reverse pharmacology is a cutting-edge technique for expedited medication development because of this. assessing

medication trials while conducting an exploratory investigation. to understand the mechanistic interpretation of concurrently conducted clinical investigations. Ayurvedic medicine treats multi-target disorders using a methodical strategy. Consequently, the most promising treatment for multi-target disorders is Ayurvedic medicine. Certain conditions, like diabetes and cardiovascular disease, require long-term care. When modern medicine and herbs are combined, major negative drug interactions can occur. Consequently, compelling data is needed to demonstrate safety.(5) Reverse pharmacology can discover the potential of herbal medicine and become an innovative tool for drug discovery. With several chronic disease treatments, there is an increasing demand for herbal treatments(6)(7). Reverse pharmacology is not only used to find out the hidden potential of the new drug, it is also useful in figuring out the new uses of the old drug. Herbal medicine phytochemicals act as scaffolds for modification(8).

In this research, the writers examined [3,4,5,6,7] a few of the most current research and papers that examine the function of discovering new drug by using pharmacology in reverse approach.

Definition of reverse pharmacology approach:

Discipline of combining recorded medical and experimental hits with leads from exploratory transdisciplinary research to develop ideas into potential medications through clinical and experimental investigations is known as reverse pharmacology.(9) Reverse pharmacology (RP) is An innovative plan that can be extensively used validate therapeutic effects on Ayurvedic medications, which have been used for centuries. The creativity of RP is intended to combine the knowledge of thorough safety and efficacy documentation with the knowledge of conventional treatments. RP involves different stages starting with experiential knowledge/data, preliminary investigation, and relevant studies that combine clinical and experimental methods leading to the seclusion of active ingredients. Taking inspiration from this RP procedure, the drug, fennel seed has been chosen for the proposed study (8). Reversing the path from lab to clinic of research to one of the labs to clinics is the focus of the reverse pharmacology discussed here. The discipline of incorporating recorded clinical events as well as practical findings into leads via multidisciplinary exploratory studies and then creating those to potential drugs through rigorous clinical and preclinical studies is called "reverse pharmacology.". Safety is still most crucial place to start in this process, and effectiveness is now determined by validation.(10).

Background:

Approximately 70% of people on the planet still use traditional medical systems (TMM). Over 500 million Indians use homoeopathy, Unani, Ayurveda, Siddha, and other complementary and alternative medicine (AYUSH) (Raut, 2013). The medicinal properties of plants make up the majority of the herbal therapies in the TSM pharmaceutical manuals. On a worldwide scale there is an increasing need for safe herbal treatments to treat a range of acute and chronic illnesses. Despite their widespread use, herbal drugs' evidence base is deemed insufficient. Different kind of evidence and a different strategy are what these therapies require. These traditional natural remedies are frequently declared statistically to be "not convincing" by "Cochrane reviews" after being removed from their contextual matrix and the topic of large statistical investigations. It is not just a matter of tossing a coin; pharmacology in reverse has fundamentally a cross-disciplinary search practical meaning. With RP, unique effort which provides an important change in a novel medication innovation process, the potential of commonly utilised TSM drugs/plants may be explored. The creativity of RP is intended to combine the knowledge of thorough safety and efficacy documentation with the knowledge of conventional treatments. Experimental knowledge and information, exploratory study, and pertinent clinically and interventional research were the three stages of RP. The RP strategy, which is 90 novel methods in Pharmaceutical Discovery carried out from "bedsides to benches," differs from traditional drug discovery and development. Further applications of established medications or monitoring a novel, unobserved signal of a potential therapeutic target may potentially benefit from it. Traditional medicines' therapeutically unique biodynamic activities could lead to new discoveries in the fields of biological sciences and biomedicine. Additionally, the phytoactive compounds can offer new chemical frameworks for structural alterations on specific therapeutic objectives. Therefore, RP can serve two purposes: it can provide new chemical entities (NCEs) to medicinal chemists and serve as an inspiration for new medications derived from traditional cures..(11)

History Reverse pharmacology approach:

The term "reverse pharmacology" originated in India. in the 1950s to produce pharmaceuticals from Ayurvedic treatments; nonetheless, it still followed the traditional method of isolating substances for more research. The Chinese also supported this idea at the time.(12)

Reverse pharmacology: new models

For NCE, the traditional route for drug discovery and development must follow a rigorously linear sequence of lengthy pre-clinical and clinical trials. The RP route, on the other hand, is a drug research and development cycle model. Its foundation is the recorded human experience in conventional medicine. Subsequently, a small sample of patients using a standardised synthesis and final goals for safety and efficacy can start the dose seeking investigation. Studies in vivo and in vitro might be initiated concurrently to comprehend the product's mechanism of action and drug-like activity. It might even be necessary to develop brand-new models that are comparable to the therapeutic outcomes seen at the bedside. Adopting epistemology-sensitive research methodologies is likewise being made more difficult by this circumstance. Validity principles must be taken into account while using research and statistical techniques responsibly. The internal as well as external validity of evidence-based medicine (EBM) must be taken into account, with a focus on logical research methods and the capacity to generalise study results. Three sorts Consensual, congruent, and contemporaneous validity requirements must be taken into account while analysing theoretical underpinnings of Ayurvedic m the occurrence at medicine and its the past of application. Congruent validity is the examination of the phenomenon at several biological levels organisations; concurrent validity is the simultaneous evaluation of the biological plausibility of the Ayurvedic description and data from the biomedical sciences; and Validity that is consensual is the agreement between practitioners of Vaidyas. The RP strategy is developing to promote integrative management using both medications and non-drug measures by carefully balancing drug-targeted screening with personalised natural medicine..(13)

Reverse pharmacology approach scope :

Understanding the principles of action at various levels of biological organisation and optimising the safety, efficacy, and tolerability for leads in natural goods according to pertinent science are the goals of reverse pharmacology.(9)

Why is Pharmacology in reverse approach important?

Reverse pharmacology, commonly known as target-based pharmaceutical discovery, has study of the potential therapeutic benefits of changing the course of a particular protein of interest that is hypothesised influence illness. The next step entails examining chemical libraries containing tiny compounds to find substances that bind to the target with a strong connection. Drug discovery process then begins using the hits from these screens. Following the human genome's sequencing, which made it possible to clone and synthesise vast amounts of purified proteins quickly, this technique gained popularity. Nowadays, this approach is the most used one for finding new drugs. In contrast to traditional (forward) pharmacology, the reverse pharmacology technique uses recognised.(14)

The present paradigm for drug discovery is characterised by expensive development, postmarketing withdrawals, and a high attrition rate. With a predetermined plans, drugs have been haphazardly appearing "from bedside The important science of drug development for safety, effectiveness, and mechanistic knowledge comes after drug discovery at the bedside in reverse pharmacology (RP). A transdisciplinary structured path like this can investigate the vast potential of innovative medications. Novel pharmacological scaffolds may be created from the phytoactives.

Benefits of Reverse pharmacology approach:

Approaches to reverse pharmacology rely on thorough data documentation and investigation of preclinical and clinical study data, which is then translated into the identification of possible drug candidates as particular molecular targets.(10) The amazing tale of the drug Jeevani started when a local tribe took a group of inquisitive Indian scientists trekking to a medicinal plant. Under the direction of Dr. Palpu Pushpangadan, this team of scientists identified the active components in *Trichopus zeylanicus* that are responsible for its energy-boosting properties. When this invention was licenced to the Indian company Arya Vaidya Pharmacy approximately thirty years ago, the Dr. Pushpangadan Institute split fifty percent of the US\$50,000 licence fee and two percent (roughly US\$5,000) of the annual royalties with the Kani indigenous tribe.

Drug sales average roughly \$230,000 USD annually. This instance is a great illustration of how a benefit-sharing scheme based on intellectual property may revitalise indigenous communities endowed with a wealth of traditional knowledge. It changed clinical practice by implementing the concepts of reverse pharmacology.(15)

Stages of Reverse pharmacology approach:

Innovative methods that can expedite drug development, such as reverse pharmacology, are needed for the development of herbal drugs. This is so because plants that are previously employed in Ayurveda are chosen through reverse pharmacology. Following that, these medications are assessed in preliminary clinical trials. In order to determine molecular explanations for the clinical action, experimental research can be conducted concurrently.(16)

The transdiscipline of reverse pharmacy includes 3 phases:

- 1) The experiential phase comprises thorough record-keeping and thorough documenting of clinical observations of the biodynamic effects of standardised Ayurvedic medications.
- 2) Para-clinical research in pertinent in vitro and in vivo models to assess the target activity, as well as exploratory investigations for tolerance, medication interactions, and dose-range determination in ambulant patients with specific subsets of the condition.
- 3) To find and confirm the reverse pharmacological correlates of Ayurvedic medicine safety and efficacy, basic and clinical experiments at multiple levels of biological organisation are needed.

A retrospective treatment-outcome study was used to choose a remedy for development as the first phase. A dosage-escalating clinical experiment that demonstrated a dose-response phenomena and assisted in determining the safest and most effective dose was the second step. A randomised controlled study was the third step, in which the phytomedicine was compared to the conventional first-line treatment. Finding active chemicals that can be utilised as markers for standardisation and quality control was the final step..

Stages of Reverse Pharmacology



Evidence of Reverse pharmacology approach:

Title of the Article	Author/ Year of Publication/ Ref.	Conclusion by the Author	Remarks
Using "reverse pharmacology" to create a phytomedicine with anti-malarial properties	Jacques Falquet, Bertrand Graz, and Marion L. Willcox Journal 15 March 2011 https://malariajournal.biomedcentral.com/articles/10.1186/1475-2875-10-S1-S8	The suggested approach could also be modified to create herbal preventatives, moving from good ethnomedical observation through clinical investigations.	Innovative public-private partnerships with businesses that are already proficient in producing standardised phytomedicines may also be taken into consideration..
Applying Reverse	Traditional Complement	Pharmaco-dynamic research,	It is possible to

Pharmacology to the Development of Botanical Drugs: Drawing from the Tradition of Conventional Wisdom	Medicine; Young-Joon Surh J. Oct-Dec 2011 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3943000/	pharmaceutical development, safety validation, and traditional use track records have already demonstrated the materials' safety. These investigations can be carried out concurrently with controlled clinical trials.	expedite the creation of novel medications with high efficacy and low toxicity by using reverse pharmacology.
Reverse pharmacology: expedited drug discovery process	Yatinesh Kumari, Mohd Farooq Shaikh, and Alina Arulsamy Pharmacy & Pharmacology International Journal May 24, 2016 https://medcraveonline.com/PPIJ/reverse-pharmacology-fast-track-path-of-drug-discovery.html	To better understand their effect and increase their efficacy, the herbs utilised in these medicines are screened against the target molecules that are known to be involved in the physiological effect.	Reverse pharmacology on natural goods begins and ends with humans, validating their safety, enhancing their functionality, and saving money and time.
Reverse pharmacology influenced by research on Ayurvedic medicine goods for arthritis	Ashwinikumar Raut1,*, Girish Tillu2 and Ashok D. B. Vaidya1 SPECIAL SECTION: INTEGRATIVE MEDICINE https://www.currentscience.ac.in/Volumes/111/02/0337.pdf	This article describes how specific experimental and clinical research have transformed the bedside experience in arthritis by RP into evidence. To include Ayurvedic principles and practices in a safe and effective manner for specific indications, it is necessary to comprehend and implement them in the particular protocols and models of RP.	RP method for using Ayurvedic medications to treat arthritis.

Drugs obtained by the reverse pharmacology path:

Ayurvedic experience has produced a large number of promising lead molecules, such as: Rauwolfia alkaloids for hypertension; Psoralens for vitiligo; Horrhena alkaloids for amoebiasis; Guggulsterons as hypolipidemic agents; Mucuna pruriens for Parkinson's disease; Piperidines as bioavailability enhancers; Bacosides for mental retention; Microsides for hepatic protection; Phellodendhins as antivirals; Curcumines in inflammation; Withanolides, and numerous other steroidal lactones and glycosides as immunomodulators.

Conclusion:

Plant products that have been scientifically verified and technologically standardised can be investigated more quickly with cutting edge methods like systems biology and reverse pharmacology, which are grounded in conventional medicinal expertise. As societies and people continue to find methods for changing habits, traditional medicine is an evolutionary process. Traditional medicine and ethnopharmacology are the sources of many contemporary medications..(17) RP improves the relationship, exchange of ideas, and cooperation between contemporary science and technology, conventional medicine, and contemporary biomedicine. The traditional drug development approach is costly and time-consuming, whereas rapid prototyping (RP) is cost-effective, time-efficient, and has fewer bottlenecks. Additionally, it facilitates the comprehension of various medication action mechanisms and aids in enhancing the safety, effectiveness, and acceptability of natural product leads. RP, also known as a path of pharmacology from the bedside to bench studies, is a method of drug discovery that makes use of conventional medical expertise.(18)

RP is a transdisciplinary approach that connects conventional knowledge bases with newly developed research instruments, technologies, and procedures. The long-awaited therapeutic breakthroughs may be facilitated by the RP-

based strategy to drug discovery. To expedite drug discovery and the creation of better, safer, and more potent medications, reverse pharmacology techniques must be refined and expanded upon.

Conflict of Interests:

The authors have stated that they have no competing interests.

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