Reverse pharmacology for Ayurveda-based modern medicines

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Traditional medicines emerged as a boon for the populations with strong socio-cultural and historical influences or in the absence of alternative or complementary therapies. Ayurveda, an Indian system of medicine, built remarkable knowledge over the practice of several thousands of years. This gold mine of clinical observations is attracting global pharmaceutical corporations to fuel their investigational drug pipelines. What's good in this for the modern medicines, the system of Ayurveda, and public health? Let's find out.

Drug discovery of modern times: probability vs. strategy

Drug discovery is getting more challenging even after the emergence of cutting-edge technologies. Pharmaceutical innovators are increasingly aware of the societal expectation about the safety and efficacy of medicinal products. The trend of post-approval or post-marketing remittance of drugs is still not declining, which is a cause of concern. Practitioners claim that the safety of new molecular entities remains uncertain for many years after market introduction (Lasser et al., 2002). Cost, lengthy timelines, and resulting accessibility issues are the most storied characteristics of conventional drug discovery processes. The incidents of drug resistance demand biopharma innovators to take on the mantle of accelerating drug discovery pipelines.

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We believe that Ayurveda's clinical findings might help address these four-square challenges.

Reverse pharmacology: Traditional medicine-inspired drug discovery strategy

When a curious group of Indian scientists on trekking was introduced to a medicinal plant by a local tribe, an extraordinary story of a drug called Jeevani began. This group of scientists was led by Dr. Palpu Pushpangadan, which isolated the active ingredients responsible for energy-boosting activity from *Trichopus zeylanicus*. About three decades back, when this technology was licensed out to Indian company Arya Vaidya Pharmacy, Institute led by Dr. Pushpangadan shared 50% of the US$50,000 license fee and 2% (around US$5,000) annual royalties with that local tribe of Kani. Drug sales record about US$230,000 a year (WIPO Magazine, 2004; Padma, T. V., 2005). This case is an excellent example of how a benefit-sharing

model using intellectual property can revamp local communities with rich traditional knowledge. It adopted reverse pharmacology principles by transforming clinical observations and traditional knowledge of the locals into commercial drug products for global markets. This story inspires several practitioners to adopt such a strategy.

Reverse pharmacology is a rigorous scientific approach of integrating clinical observations, transforming experiential observation into leads by transdisciplinary exploratory studies, and developing leads into drug candidates or formulations through robust preclinical and clinical research [Patwardhan & Mashelkar, 2009]. Conventional approaches route the journey of drugs from laboratory-to-clinic. Reverse pharmacology, though not completely comparable to the traditional drug discovery process, follows an alternative pathway from clinic-to-laboratory and again back-to-clinic [Fig. 1]. As Ayurvedic formulations have been used for thousands of years, their clinical experiences can catalyse drug discovery if recorded rigorously. The seeds of Indian reverse pharmacology sowed with the study of two physicians, Dr. Kartick Chandra Bose and Gananath Sen [1931], who investigated the antihypertensive effects of Rauwolfia serpentina along with associated side effects such as depression, parkinsonism, etc. A seminal paper by Dr. Rustum Jal Vakil [1949] on applications of R. serpentina in the treatment of hypertension caught the eyeball of a western pharmacologist. The parallel contributions of Sir Ram Nath Chopra, who has been acclaimed as the Father of Indian Pharmacology, arouse interests in Indian medicinal chemists and pharmacologists.

A little strategy makes a world of difference

Over the decades, the practice of reverse pharmacology has shown unique features and potential. When Sen and Bose could demonstrate the antihypertensive and side effects of R. serpentina, peers took findings to discover a series of antidepressants and anti-Parkinsonian's actives. Reverse pharmacology established that drug discovery is not restricted to developing new molecular entities and developing the same from scratch. Long-term, large-scale application of such Ayurvedic actives in society assures clinical safety and efficacy needs significant attention.

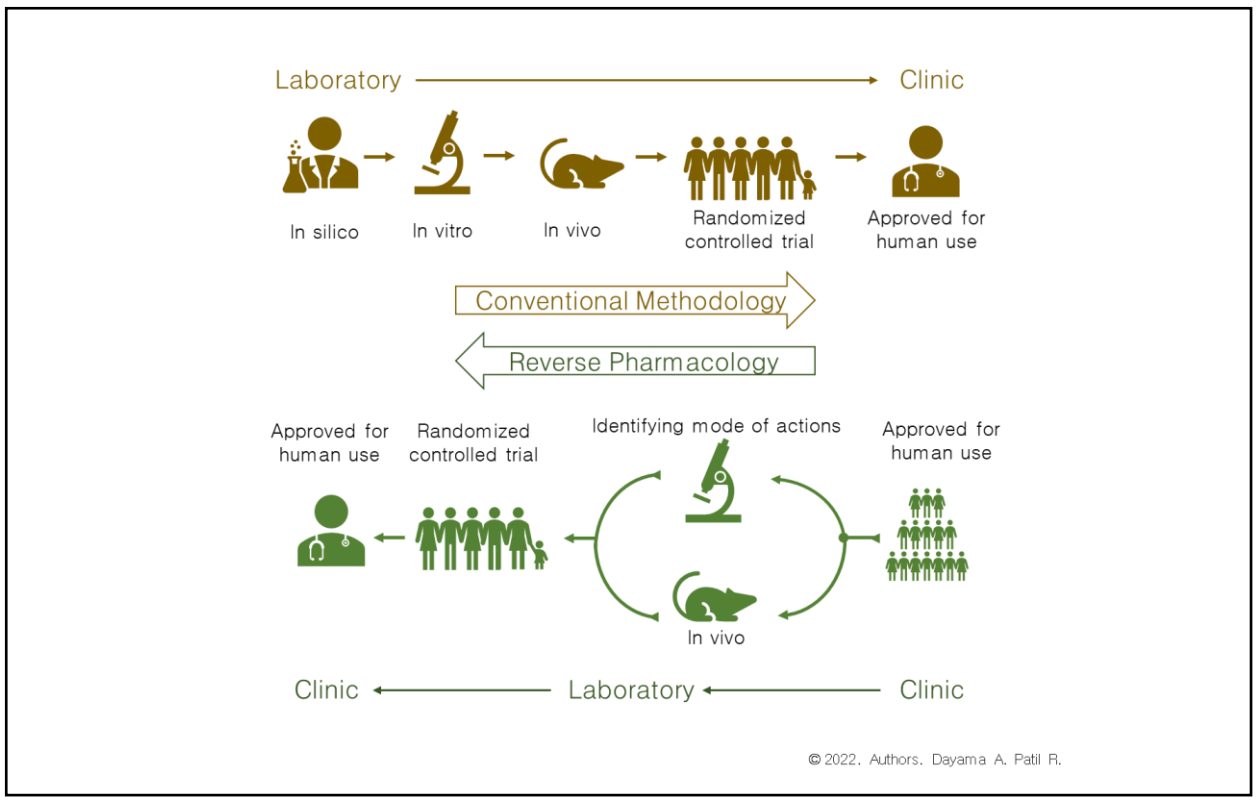

FIGURE 1

The illustrative flow of practices followed in conventional drug discovery and reverse pharmacology

Reverse pharmacology comes with several benefits and is a potentially preferred choice in drug development. Even though both are not fully comparable and replaceable, their adoption needs careful considerations. Amongst the foremost, reverse pharmacology cuts the time of drug discovery from twelve years to five years or less, and that too for reduced costs [Padma, TV, 2005]. Such ambitious timelines can be accomplished for a very stated reason as the ayurvedic drugs are already in use, exploratory clinical examinations, and mechanistic explorations can be done parallelly [Puranik & Patwardhan, 2012]. Recently anti-malarial herbal therapeutic development took six years for designing and implementation of reverse pharmacology approach in Mali [Willcox et al., 2011]. Costs of such conventional drug development hamper the accessibility of essential medicines affecting the poorest public the most. This can be tackled through reverse pharmacology, limiting the massive screening for newer leads. Ayurvedic drugs potentially follow polypill mechanisms as they adopt a systems biology approach and are promising for treating multi-target diseases. These medicines can be better alternatives for such conditions due to their multi-ingredient synergistic and prophylactic formulations [Kumar et al., 2008; Verpoorte et al., 2005].

With the appropriate documentation of clinical experiences from Ayurvedic therapeutics, practitioners can also facilitate repurposing existing drugs. Examples include forskolin for obesity and atherosclerosis or berberine alkaloids for dyslipidemia [Patwardhan & Mashelkar, 2009; Kong et al., 2004]. Yet another essential benefit relates to the issue of drug resistance. In the race of disease eradication, continuous use of existing medicines leads to drug resistance against pathogens, and relatively dry drug pipelines pose an urgency that needs to be addressed. If adopted strategically, reverse pharmacology may bring in newer medicines, reducing the burden on existing therapies and elongating their lifespan. As mentioned earlier, safety remains the primary point of initiation, and validation of efficacy takes centre stage. Large-scale clinical usage in society further assures the availability of safer leads for pipeline forward. Even after approval from regulatory agencies or

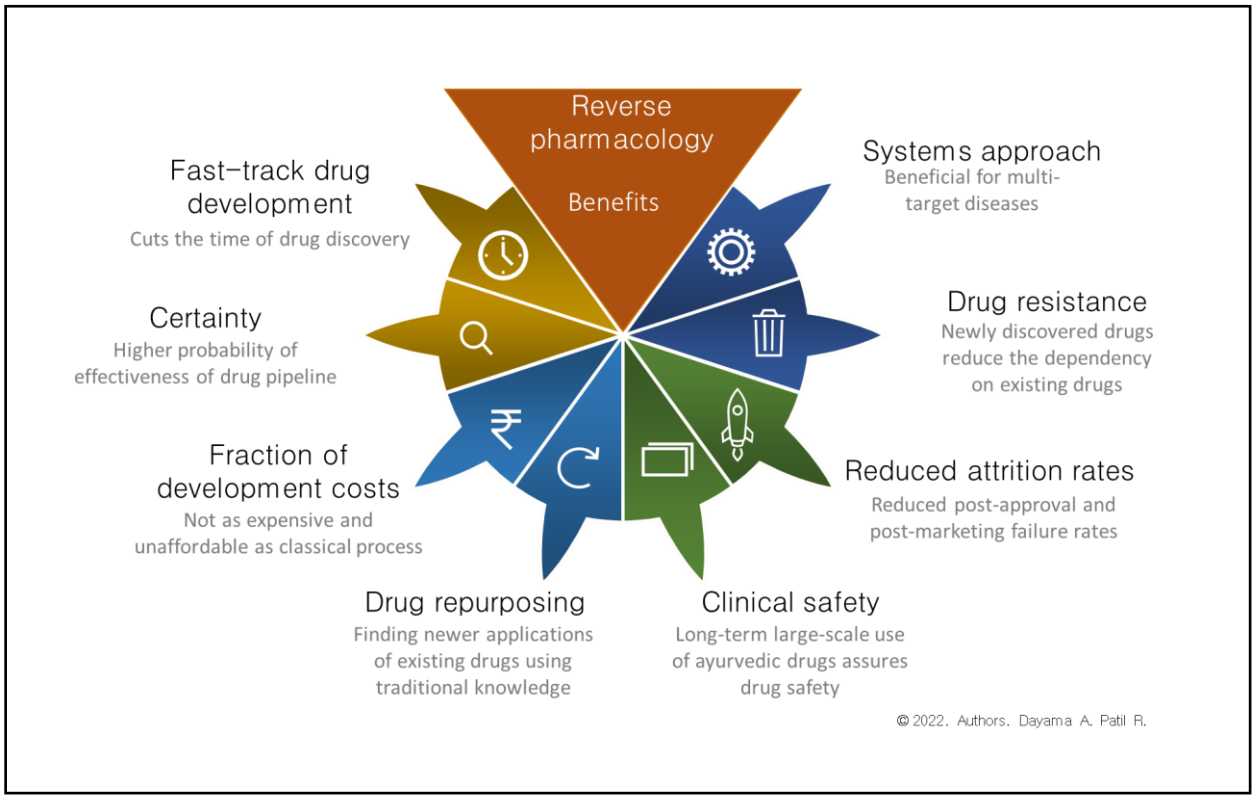

FIGURE 2

The benefits of reverse pharmacology over conventional drug discovery

market introduction, positive signs of the reduced attrition rate are observed in contrast to the conventional drug discovery processes [Patwardhan & Mashelkar, 2009]. With the ready demonstrations of the clinical effects of herbal formulations, the biopharma companies remain assured of the safety of the drug candidates. Such confidence in developing treatments remains lower with the typical drug discovery process.

Empowering reverse pharmacology: policy perspectives

About 70% of rural populations of India, China, Egypt, and Sudan, whereas about 17.7% of Americans use herbal therapeutics [Puranik & Patwardhan, 2012]. This vast capacity is an opportunity to generate the latest clinical empirical data. Various laboratories or private companies should take advantage of this enormous knowledge source. Having said that, many of these medicinal plants cannot be traced back to individual communities, as seen in the case of the Jeevani drug. Hence, there is a need for better frameworks and guidelines to extend monetary and non-monetary benefits to deserving communities.

Widespread acceptability of conventional drug discovery is achieved through dedicated and validated explorations of suitable mechanistic pathways for active ingredients of therapeutic pills at molecular levels. Similar elucidations of mechanistic studies are needed for herbal medicines. As the Ayurvedic medicines tend to follow the synergistic, systems-based mode of actions, the whole systems-based mechanical approach needs to be explored [Puranik & Patwardhan, 2012]. For the entire exercise, the importance of well-documented clinical observations and patient feedback cannot be emphasized enough and should be the utmost priority of practitioners. Dr. Lele [2010] points out that patient feedback often plays a critical role in early discoveries that are directly related to the time-lags between proof of pharmacological action and identification of active principle, and further, identification of their mechanisms of actions. As there are thousands of medicinal plant species of interest, there is a need for centralised databases monitoring the plants under investigation. One such database is available at the National Botanical Research Institute in Lucknow that catalogs tribal traditional knowledge of about ten thousand medicinal plants [Padma, TV., 2005].

The government of India established a dedicated Ministry of Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homoeopathy (AYUSH) to facilitate Indian systems of medicines in 2014, which functioned as a department earlier under the aegis of the Ministry of Health and Family Welfare. The government of India took several steps to build a culture of herbal drug development in the past two decades. One of such steps is the New Millennium Indian Technology Leadership Initiative (NMITLI), administered by the Council of Scientific & Industrial Research (CSIR). This effort brought industry-academia closer across cutting-edge technologies, including herbal drug discovery, particularly for psoriasis, osteoarthritis, hepatitis, and diabetes [CSIR, 2022]. Indian Council for Medical Research (ICMR) also put forward a step in establishing the Advanced Centre of Reverse Pharmacology, focusing on malaria, sarcopenia, and cognitive decline. Recently the Maharashtra University of Health Sciences (MUHS) has brought a postdoctoral fellowship training program and diploma course in Reverse Pharmacology [Vaidya, ADB, 2014]. Interestingly, the Ministry of AYUSH established a research centre at the University of Mississippi, USA, called the Indo-US Center for Research in Indian Systems of Medicine. This centre focuses on scientific validation and dissemination of AYUSH products to meet global concerns on the safety, efficacy, and quality of such products [UM News, 2009]. Also, internationally, India took the lead in encouraging dialogue on traditional medicines with the US. India also established databases like TKDL and FRLHT or decision support systems like Ayusoft to convert traditional knowledge or classical Ayurvedic texts into a comprehensive knowledge repository.

With this great effort, India should not become complacent in the ripening fruits of its age-old knowledge institutions. Indian practitioners of reverse pharmacology should integrate the high-throughput screenings, combinatorial chemistry, and explorations of genomics and proteomics with their studies (Vaidya, A., 2006). Few researchers argue that

instead of randomized controlled trials, strategies of pragmatic clinical trials may be better suited for traditional medicine-inspired reverse pharmacology approaches (Patwardhan & Mashelkar, 2009). Though establishing a dedicated Advanced Centre for Reverse Pharmacology is a unique and appreciable step, India needs to extend the circuit of such dedicated research centres considering the transdisciplinary nature of reverse pharmacology. Laboratories performing research on natural products on medicinal herbs and their mixtures need to be promoted. Notably, there is a need for infrastructural institutions such as incubation facilities for the specialised deep-tech start-ups in the domain of interest; clinical repositories for preservation, maintenance, and delivery-on-demand of cell lines, plant extracts; special facilitation centres for standardising operating procedures for collection, analysis, reporting, evaluation of herbal compositions; and centre for monitoring and guidance on good manufacturing practices, good clinical practices, and integrity and ethics of preclinical and clinical assessment of herbal products. Implementing stringent and well-guided frameworks for evaluating such products will enhance the acceptability among societies globally.

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