Reverse pharmacology of Ayurvedic drugs includes mechanisms of molecular actions

Sir,

In his article "Beyond reverse pharmacology: Mechanism based screening of Ayurvedic drugs," Dr. R. D. Lele, the eminent teacher of modern medicine and scholar of Ayurveda, urges us to include advances in biomedical sciences for screening of Ayurvedic drugs.[1,2] However, as he has not cited any of the original articles and references on Reverse Pharmacology (RP),[3-7] it seems that the experimental stage of RP has been overlooked. Here, an attempt is made to correct the impression that molecular screening of Ayurvedic drugs is beyond RP, and indicate which aspects of Ayurveda may truly lie beyond the current state of RP.

Lele cites quite a long list of available receptors and transporters including specific radiolabeled ligands. In view of his being a leader of nuclear medicine, any initiatives in the direction of using labeled ligands or candidate drug molecules are welcome suggestions. But the list does not provide any hints as to how Ayurvedic drugs in their complex form can be subjected to such blind screening. Even with significantly large numbers of molecules synthesized by combinatorial chemistry and with high-throughput screening, this path to drug discovery has not been very productive. That is why major pharmaceutical companies have relatively dry drug pipelines, raising the urgent need for new approaches.[8] Patwardhan and Mashelkar emphasize this point, while advocating RP for traditional medicine inspired drug discovery.[4] However, for drug discovery through RP and other approaches, it would be desirable to create a database of receptor binding sites of important phytoconstituents of Ayurvedic origin. This exercise, being a relevant part of drug discovery, is clearly not a stand-alone means to that end. We should not forget that several New Chemical Entities and biotech products binding receptors *in vitro* have failed in clinical trials due to the impact of kinetic-dynamic factors *in vivo*.

The author describes molecular biology and molecular medicine as 21st century paradigms. However, the leaders in molecular medicine themselves are rapidly adopting systems biology, and more integrative approaches.[9,10] Under these circumstances, an organized RP path would be a productive new paradigm for drug discovery, with its initial robust clinical observations, and objective markers during its experiential stage. For example, in a recent study with *Nyctanthes arbor-tristis* in patients with malaria, the parasite cure was confirmed by the disappearance of the parasitic DNA with polymerase chain reaction; the marked clinical improvement within 48 hours was accompanied by a significant drop in Tumor Necrosis Factor-α. The exploratory studies included screening of the plant extract against sensitive and resistant strains of *Plasmodium falciparum in vitro*.[11,12] This exemplifies that the advances in markers can be made use of at each stage of RP. Currently, efforts are to isolate the active molecule, which would eventually facilitate mechanistic studies in molecular parasitology, during the RP experimental stage.

Dr. Lele has cited *Rauwolfia serpentina*, in particular reserpine, as a unique molecule illustrating diverse activities on vesicular mono-amine transport. But the loss of opportunity in research on biogenic amines was a gap of 20 years between the discovery of *Rauwolfia serpentina* as an antihypertensive, and the isolation of reserpine.[13,14] During these two decades, when management of hypertension did not have many alternatives, thousands of patients died of complications. The side effects of *R. serpentina* observed by Sen and Bose, *viz.*, Parkinsonism, depression, and galactorrhea, were the fore-runners of major drug discoveries—levodopa, tricyclic antidepressants, and bromocriptine. These discoveries could have been expedited if an organized RP path had been available. We now have an opportunity to study other documented field observations with similar scientific rigor. Some lessons to further develop and

Table 1: Correlation between guna-karma and mechanistic targets of Ayurvedic drugs

Medicinal plant	Clinical usage	Guna-karma	Mechanisms
Berberis aristata	Conjunctivitis	Tikta, kaphanashaka	Intercalates DNA
Adhatoda zeylanica	Asthma, cough	Ruksha, Kasaghna	Disulfide bonds
Commiphora wightii	Atherosclerosis	Lekhana, Medohara	Farnesoid X receptor
Curcuma longa	Inflammation	Ushna, Shothaghna	NF-kB, COX- 2, VEGF
Phyllanthus emblica	Aging, Diabetes	Tridoshahara, pramehaghna	Increase SOD mRNA, reduced DNA damage

expedite the process are as follows: 1. To understand and give importance to robust findings in observational therapeutics; 2. To carefully choose *in vitro* and *in vivo* models relevant to the clinical endpoints, or even to evolve novel models as needed; 3. To evolve a collaborative R and D network for quality, safety, and efficacy of whole plants and/or their extracts and/or their active principles depending on use. These research approaches have been depicted as a figure for clarity.[6]

As an eminent leader and teacher of modern medicine, the author has rightly emphasized that advances in phytopharmacology need to be utilized in Ayurvedic drug research. But there is also a need to emphasize an understanding of Ayurvedic epistemology and the principles of *Dravyaguna vigyan*, while embarking on modern drug research.[14] Such an approach is not easy, and would involve innovative thinking beyond the current state of RP. As Systems Biology is becoming central to understanding the complexity of human clinical phenomena, early attempts at modeling Systems Ayurveda would enhance the incorporation of the basic nature of Ayurvedic drug actions.[5,15] As an example, Table 1 lists a tentative correlation between clinical usage, guna-karma, and mechanisms.

RP relies on known and serendipitous clinical phenomena resulting from simple or complex Ayurvedic interventions. The endeavor to study well-documented findings would provide not only understanding in terms of identified molecular mechanisms, but will hopefully open up new domains of knowledge in Life Sciences. Unfortunately, RP is a new transdiscipline and has only one Advanced Centre of Research established by the Indian Council of Medical Research.[16] The new training programs for Vaidya—Scientists as well as for RP are planned with an eye to orient therapeutic research to Ayurvedic epistemology and the ontology of RP.[17,18]

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Website: www.jaim.in

DOI: 10.4103/0975-9476.82512