

Reverse pharmacology for antimalarial plants goes global

Sir,

A recent issue of the Malaria Journal has been dedicated to the research and development of natural products for treatment of malaria. All the articles in the issue are interesting. The article on Reverse Pharmacology (RP) by Willcox *et al*^[1] is of particular interest, which suggested that this transdiscipline of RP has global appeal. The RP path, as Willcox *et al* have rightly mentioned in their article, has originated in India for new drug discovery and is based on Ayurveda, India's ancient traditional system of medicine. However, the statement of Willcox *et al* supported by the reference of Patwardhan and Mashelkar^[2] that "RP still involves classical pathway of isolating compounds for further development" is true only to a certain extent. RP in India focuses mainly on the development of Ayurveda-inspired standardized formulations, the safety, and activity of which is implied through its long history of usage. Several other paths may be considered for the development of drugs from Ayurvedic therapeutics and natural products, one of them is isolation and identification of active compounds.^[3]

It was notable to see that Merlin Willcox and group have used RP approach to develop antimalarial complementary formulation from the ethnobotanical/folklore leads. In deference to African folklore uses of medicinal plants for fever, the Ayurvedic approach to Malaria (*visham-jwara*) makes use of diagnostic components (*nidan*) and Ayurvedic Pharmacology of Medicinal plants (*dravya-guna-vigyan*).^[4,5] Classical Ayurvedic descriptions of ailments and their management besides a long tradition of usage of medicines by Ayurvedic physicians form a basis for the selection of the medicine for evaluation through RP. Willcox *et al* evolved a standard score system to prioritize a plant from folklore practices. This includes meticulous analysis and scoring of ethnobotanical data for (i) frequency of citation of a plant, (ii) efficacy *in vitro* and *in vivo*, and (iii) safety

and activity based on retrospective treatment outcome (RTO) study.^[6] Ayurveda-inspired RP on the other hand provides foundation of long-term experience of clinical usage, Ayurvedic-pharmacodynamic rationale and evidence generated through current biomedical integration for the development of drugs.

Here we illustrate RP approach with respect to the *Nyctanthes arbor-tristis* Linn. (Parijat) for the antimalarial activity. The plant, indicated in Ayurveda for the treatment of *visham-jwara* is used by Ayurvedic physicians for recurrent fevers and hepatosplenomegaly.^[7] Parijat has been extensively studied by our group through the three stages of RP (experiential, exploratory, and experimental) as defined by Vaidya ADB in 1990s.^[8-10] Some aspects of this work were presented by Vaidya ADB at the International Workshop on Screening and Preclinical Development of Antimalarials at NIH, Bethesda.^[11] The experiential study of the paste of leaves of *N. arbor-tristis* in 120 patients showed ~80% clinical and parasite cure.^[12] The unique clusters of symptoms, namely, chills, rigors, nausea, vomiting, body ache of *visham-jwara* also showed a significant relief. Further exploratory clinical study with objective markers in 20 patients showed early clinical response with gradual parasitic clearance. There was a statistically significant reduction in the morbidity score monitored for the severity of the above-mentioned symptoms. Detailed biochemical investigations for organ function safety and for the mechanism of action were done in these 20 patients. Early clinical response was associated with increase in platelet count, decrease in lactic acid; the key markers of severity of malaria. There was also a significant reduction in circulating TNF- α and other proinflammatory cytokines with the given fixed dose of the paste. In this study at very early stage of RP sophisticated science was used as the disappearance of the malarial parasite was confirmed by the polymerase chain reaction for parasite DNA.^[13] Early *in vitro* study conducted concomitantly during the exploratory phase showed antiparasitic activity against drug sensitive (3D7) and drug-resistant (Dd2) *Plasmodium falciparum* strains with nonpolar extracts of leaves at minimum inhibitory concentration (MIC₅₀ 25–35 μ g/mL).^[13] Currently extensive experimental studies have been taken up both for the development of standardized formulation and identification of compounds for both antiparasitic and anti-inflammatory activity. After systematic extractions of leaves different extracts and fractions are being further studied for antiparasitic and anticytokine/anti-inflammatory activities.

In India, pharmacology of medicinal plants from Ayurveda has evolved during the last century. The pioneering work by Sir Ramnath Chopra, an experimental

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pharmacologist, and Gananath Sen, an eminent Ayurvedic clinician, through astute observations indicated the need for organized research efforts.^[10] RP is now getting formally established in India as an organized transdiscipline through efforts by the Indian Council of Medical Research (ICMR) Advanced Centre of RP in Traditional Medicine under Medical Research Centre-Kasturba Health Society (MRC-KHS). However, perception of RP appears to be mystifying. The recent article, "Beyond Reverse Pharmacology..." by Lele, emphasizes a need of approach for mechanism-based screening of Ayurvedic drugs.^[14] However, the experimental phase of RP does include understanding of mechanisms and use of advanced science. In the subsequent issue of *JAIM*, Namyata Pathak has rightly elucidated this through the "letter to editor" in response to the article by Lele.^[15] Willcox *et al* have used the term RP for their work on folklore medicine. Here we exemplified Ayurveda-RP through our study of *N. arbor-tristis* for malaria to highlight the differences in the study by Willcox *et al*. Such communications are necessary for expanding the understanding of RP. Besides this, a recent, to be added national "ICMR workshop for Training in RP" conducted by MRC-KHS and state-level research fellowships in RP announced by the Maharashtra University of Health Sciences (MUHS) will certainly help to appropriately comprehend and further develop this transdiscipline of RP for Traditional medicine.

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