Reverse pharmacology effectuated by studies of Ayurvedic products for arthritis

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Reverse pharmacology (RP) is a trans-disciplinary path for drug discovery and development from bed-side observations on drug effects to bench-side experiments. This approach generates evidence of safety and efficacy at different levels of biological organization, ranging from cell to community. Eventually the innovative integration of research methods will be translated back to the bedside as a new drug. The experiential wisdom of traditional systems like Ayurveda is scientifically explored by systematic RP. This is meant to enrich modern medicine, by the relevant application of the drug discovery sciences. The evidence by RP would also help to rationally understand Ayurveda. This article highlights how the bed-side experience in arthritis has been translated by RP into evidence by defined experimental and clinical studies. There is a need to understand and apply the basic principles and practices of Ayurveda in the specific protocols and models in RP so as to truly integrate effective and safe usage for definite indications. The article also discusses the RP approach for Ayurvedic medicines used for treatment of arthritis.

Keywords: Ayuveda, integrative medicine, repurposing drug, reverse pharmacology.

Introduction

THE development of clinical pharmacology and molecular approaches has helped in the discovery and development of new drugs for the current therapeutics over the last 50 years. The ongoing advances in life sciences, systems biology and medicinal chemistry are being adopted for drug discovery and development. Notwithstanding the combinatorial chemistry, high-throughput assays for target-specific effects, biotechnology products and a huge expenditure for new drugs, there is often disillusionment due to the high attrition rate of new chemical entities (NCEs) and several recalls of the marketed blockbuster drugs[1]. Withdrawal of rofecoxib due to cardiovascular risk represents a lacuna in the safety aspects of the current drug discovery process. The best minds in drug research have started looking for a shift in the current dominant paradigm of drug discovery path from the bench to the bedside[2]. Even repositioning of longstanding drugs for new indications is being invoked[3]. The 2015 Nobel Prize in Physiology or Medicine to Tu You You, a professor of traditional Chinese medicine (TCM) for her pioneering work on quinhao (*Artemisia annua*) has resulted in active discussions to look for new drugs from another rich tradition like Ayurveda, through observational therapeutics (OT)[4], Ayurvedic pharmacoepidemiology (AyPE)[5] and reverse pharmacology (RP)[6]. Ayurveda basically is founded on an integral approach to human health and its disturbances of the triad of body, mind and spirit.

Institutionalization and globalization of Ayurveda as a healthcare delivery system demand scientific evidence for its wider acceptance and scale-up applications. Current evidence-based medicine necessitates information on safety and efficacy that has to be predictable for a precise indication. The actions of common plants will have to be understood. Also, in view of some of the extinct or endangered plant species, several traditionally used formulations may have to be redefined with rational substitutions or exclusions of some of the ingredients. Other products can be gainfully studied for newer indications. Besides the systematized knowledge and pharmacopoeia of Ayurveda, many more natural products are used in local and global health traditions. Generating evidence base for these experienced remedies demands a novel integrative path of drug development.

RP approach is a sophisticated transformation of the conventional path of drug discovery and development. The applicability of RP to traditional remedies facilitates drug discovery from natural products used in humans for a long time. Unlike the conventional pharmacology path of new drug discovery from NCEs, in the RP path the initiative is at the bedside. The path, being from 'the bedside to benches' instead of 'benches to bedside', explains the adjective 'reverse'. RP demands trans-disciplinary experts', viz. traditional medicine specialist, clinical investigator, basic scientist, clinical pharmacologist and expert in drug discovery science. RP is defined as 'the science of integrating documented clinical/experiential hits, into leads by trans-disciplinary exploratory studies and further developing these into drug candidates by experimental and clinical research'. The scope of RP is to

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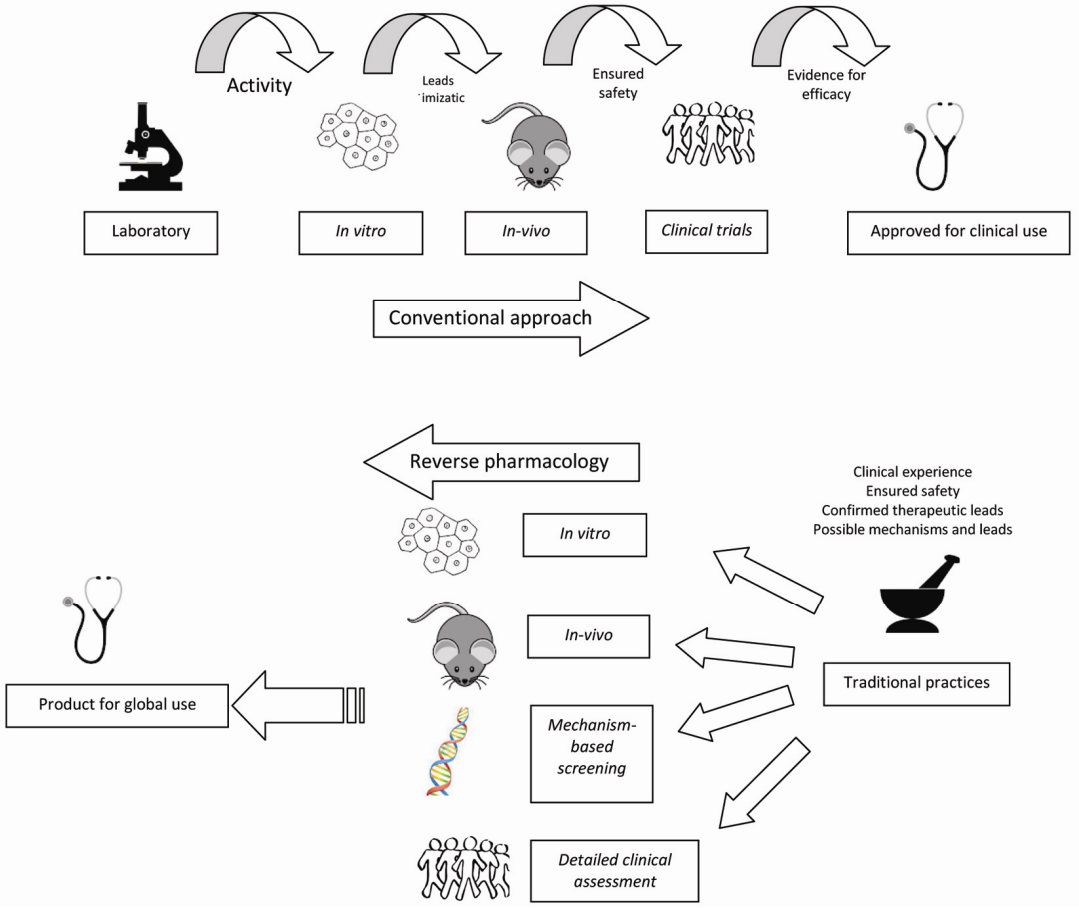

Figure 1. Conventional and reverse pharmacology approaches for natural product based drug discovery.

understand the mechanisms of action at multiple levels of biological organizations and to optimize safety, efficacy and acceptability of the leads in natural products, based on relevant science[6] (Figure 1).

The roots of many modern drugs can be traced to natural products/plants and their active phytomolecules[7] (Table 1). These drug discoveries have come from observations of dynamic effects of poisons, or have been resourced from ethno-medicines practices or through serendipitous findings. In the past that route was sporadic, tardy and not systematized. The path can be focused, organized and productive for safe and effective new drugs in a fast-track and cost-effective manner[8]. The pre-requisites for the success of RP are pharmaceutical excellence for standardization of plants and formulations, objective evidence of safety and efficacy, and a rapid and formal approval path by the drug regulatory authorities.

Identifying the signals from experiential noise

The experiential domain of the product–utility relationships in context of Ayurveda is a vast treasure enriched by the documented experiences of experts over a millennium, and the database of India's national mission on manuscripts can provide over two million of such records[9]. The challenge lies in the identification of the right hints and decisions on the correct hits and leads, for the unmet medical needs. Intuitive choices made by an astute clinician the serendipitous findings observed by a prepared mind are also welcome. Alternatively, the hints, hits and leads can be tapped strategically and consensually with several organized methods. Systematic literature search, observational therapeutics, pharmacoepidemiology, analysis of case series, $N = 1$ studies, Ayurvedic profiling and phyto-pharmacological plausibility are some such methods. These have been effectively explored and utilized to identify the right signals from the apparent background noise. The examples of *Yograj Guggulu* (*YG*) and *Amrut-Bhallatak* (*AB*) illustrate this approach.

YG, a traditional formulation of Ayurveda, was prioritized for studying its role in rheumatoid arthritis. This was not only inspired by the positive personal experiences of the investigators, but also supported by a methodic analysis of its frequency of usage in a series of cases from the hospital registry. Prima facie the product–indication relationship was compelling. The first and immediate challenge was how to systematically examine the tolerability of *YG*, with increasing doses, in healthy human volunteers[10]. This led to the first phase-1 study on

Table 1. Roots of modern drugs in natural products: biodynamic phenomena

Natural source	Observational effects	Mechanism of action	Modern drugs
Currare tomantosum	Paralysis and death	Neuromuscular block	Tubocurarine, pancuronium
Physostigma venenosum	Ordeal poison	Anticholinesterase	Neostigmine, pilocarpine
Atropa belladona	Fatal poisoning	Cholinergic blockage	Scopolamine, cyclopentoalate
Bothrops jaraca	Viper poison	Angiotensin-converting enzyme inhibitor	Captopril, enalapril
Sallix alba	Fever and pain relief	Prostaglandins inhibitor	Salicin, salicylic acid, aspirin
Digitalis purpurea	Dropsy relief	Na^+K-ATPase inhibition	Digitoxin, digoxin, ouabain
Galega officinalis	Anti-diabetic	Decreases insulin resistance	Metformin, phenformin
Catharanthus roseus	Anti-diabetic	Granulocytopenia	Vincristine, vinblastine
Penicillium mold	Anti-bacterial	Transpepetidase inhibition	Penicillin and its derivatives

any formulation of Ayurveda. Further, a long-term (6 months) study of *YG* in rheumatoid arthritis followed. With *YG*, we could study the safe therapeutic dose-range (3–6 g/day), long-term tolerability, disease-modifying potential and even withdrawal of earlier prescribed corticosteroids[11].

AB, a classical formulation, having *Bhallatak* (*Semecarpus anacardium*) as a main ingredient, was chosen for investigating its therapeutic role in osteoarthritis along with RP. The choice of *AB* was primarily made by a consensus meeting of the experts of Ayurveda and biomedicine. But the approach was subsequently refined further by a detailed analysis of the experiential as well as experimental data on the plant[12]. Another major formulation for the CSIR-New Millennium Indian Technology Leadership Initiative (CSIR-NMITLI) arthritis project was *Shunthi-Guduchi* (*Zingiber officinalis* and *Tinospora cordifolia*). It was also selected to study its potential as a herbal product, inspired from Ayurveda, compared to glucosamine in arthritis. The selection was based on literature search as well as consensus of experts[13].

Epistemology-sensitive protocols

It is essential to distinguish the structure of organized traditional systems of medicine based on a well-defined epistemology compared to the primitive world-views underlying the disparate tribal practices, without a logical base. Traditional systems of medicine such as Indian system of medicine (Ayurveda, Siddha and Unani) and TCM are considered as major healthcare traditions, founded on their respective axioms and fundamental principles[14]. Besides this, the classical scientific composition of Ayurvedic literature is driven by *Tantra-yukti* (interpretative techniques)[15]. Studies or research programmes related to such a logically founded healthcare system demand relevant innovations and amendments in the protocols according to the system-specific concepts. To maintain the trans-system objectivity, we propose specific protocols which would add value not only to the studies but also enhance the logical outcome of the projects. These protocols can be broadly categorized into 'product-specific' and 'patient-specific' (Table 2).

In a pharmacokinetics study on the acetylator status of patients with rheumatoid arthritis, we could demonstrate a positive correlation between drug side effects/disease severity with the slow acetylator status and predominantly a *Pitta*-dominant constitution (*Prakruti*)[16]. The *Prakruti* can influence drug responses. In the study on *AB* in osteoarthritis, a product-sensitive change in protocol, viz. 'vehicle for the drug administration' (*Anupana*) and 'time of the drug administration' (*Aushadhikala*) was considered crucial for better safety and efficacy[17]. In the study on tolerability and activity of *Ashwagandha* in healthy volunteers, we have observed that patient-specific variables in the protocol such as *dhatusarata* (Ayurvedic index for tissue health) and *Prakruti* are linked with an *Ashwagandha* adverse event[18].

Standardization and rationalization of pharmaceutical products

Traditionally used Ayurvedic products are manufactured according to the norms stated in the authenticated list of texts and Ayurvedic Pharmacopoeia by the AYUSH authority[19]. Although these formulations have been founded on Ayurvedic rationale, there is a wide demand for further pharmaceutical standardization and quality of these formulations. The consumers demand a reduction in the bulky doses, improvement in palatability, freedom from heavy metals/pesticides/microbes and convenient/novel dosage forms. Ayurvedic pharmaceutics need to be developed to address these demands, rather than blindly adopting the current pharmaceutical manufacture. From the scientific perspective, there is a need for the evidence of quality, safety, degree of efficacy and predictability of drug response from batch-to-batch quality control. Reverse pharmaceutics can adopt and evolve the integrative approach in standardization and quality control to satisfy the aforesaid demands[20]. This can be done without any compromise on the principles and practices of the traditional system – the product source – with the help of RP[21].

Table 2. Protocols for Ayurvedic clinical trials based on system specific concepts

Product-related	Patient-related
Ayurvedic kalpa (classical form)	*Rugna Prakriti* (patient's constitution)
Aushadhi prayoga (dosage regimen)	*Shat–kriyakala* (stage of a disease)
Aushadhi kala (dosage schedule)	*Samutthana–Vishesha* (causative factors)
Anupana (vehicle for administration)	*Dosh–Dushya–Adhishthan* (pathological factors)
Ahara – Vihara (diet and life-style regimen)	*Vyadhi Lakshana* (clinical features)

These are countable determinants not confounding variables.

The activity–property matrix (*Guna–Karma*) of Ayurveda medicines can be systematically studied using existing clinical leads. The *AB* study in osteoarthritis illustrates this case well. The classical dosage form of *avaleha* (electuary) was changed into another dosage form of *Ghana vati* (tablets of dried extract) without compromising any of the 27 ingredients and the classical method of manufacture. The basic norms of botanical identification, phytochemical standardization, assessment for heavy metals/pesticides and tests for microbial contamination were ensured. In addition, the pharmaceutical standardization of the tablet dosage form, for several specifications, was also carried out. After the demonstration of good tolerability and identifying the efficacy window of 6 weeks[22], the same product was further modified and rationalized for a subsequent 6 months study. For this study, 27 ingredients in the product were reduced to only two major ingredients – *T. cordifolia* and *S. anacardium.* These two were ingredients accounted for 90% of the composition of the original classical product. Besides both these ingredients are considered as *Rasayana* (rejuvanative/reparative) plants and are indicated for arthritis and degenerative diseases. The tablet was made more compact and easy to take. This study demonstrated disease-modifying potential of *AB* in osteoarthritis[17].

The process of drug discovery and development through RP offers a wide scope. Besides the development of standardized traditional products with predictable efficacy and safety, RP is open to develop natural products as extracts with optimized bio/phyto-actives for targeted activity. There is also immense scope of structural modifications of the chemical scaffolds, provided by the active principles, to synthesize many NCEs with enhanced activity and reduced toxicity.

Novel models in reverse pharmacology

The conventional drug discovery and development path for NCE has to go through the long pre-clinical and clinical studies in a strictly linear fashion. On the other hand, RP path is a circular model of drug discovery and development. It starts from the documented human experience in traditional medicine. One can then begin with the dose-searching study in a small sample size of patients, with a standardized formulation, with objective end-points of activity and safety. Concurrently, *in vitro* and *in vivo* studies can be started to understand drug-like activity of the product and its mechanism of action. Even new models may have to be created as analogous to the clinical effects observed at the bedside.

This situation is also posing challenges for adopting epistemology-sensitive research methods[23]. The judicious use of research and statistical methods needs consideration of the basic tenets of validity. The evidence based medicine (EBM) requires consideration of internal and external validity that emphasize rational study designs and the ability to generalize its findings. Considering the theoretical foundations of Ayurveda and history of its practice, there are three types of validity – consensual, congruent and concurrent – which need to be considered. Consensual validity is agreement between practising Vaidyas, congruent validity is studying the phenomenon at various levels of biological organizations, and concurrent validity is concurrent assessment of biological plausibility of Ayurveda description and data from biomedical sciences[24]. RP approach is evolving to strike a judicious balance between drug-targeted screening and personalized natural medicine to encourage integrative management with non-drug measures as well as drugs.

Traditional Ayurvedic formulations such as *YG* and *Gokshuradi-Guggulu* (*GG*) are commonly used for diverse arthritic conditions. Both these formulations have *Guggulu* (*Commiphora wightii*) as a common ingredient in a proportion of 50%. The role of *YG* in rheumatoid arthritis has been discussed above. However, our clinical experience shows that *GG* gives benefit in some cases of undifferentiated arthropathies. Besides this experience, we had inputs from experts in the field for a study planned to investigate the activity of selected Ayurvedic plants against microcrystal-induced arthritis (DBT project). The study demonstrated *in vitro* dissolution of monosodium urate monohydrate (MSUM) microcrystals by extracts of the plants *Rotula aquatica*, *C. wightii* and *Boerhaavia diffusa*[25]. In another study of *in vitro* crystal growth of MSUM, these plant extracts demonstrated growth inhibition[26]. In a cell-biology experiment on monocyte-derived macrophage, lipopolysaccharide was shown to release pro-inflammatory cytokines (TNF-α, IL 1β). The aqueous extract of *C. wightii* inhibited the release, suggesting a

basis of the anti-inflammatory action of the plant[27]. In a novel *in vivo* model of MSUM crystal-induced subcutaneous inflammation in Wistar rats, the inflammatory exudates were reduced by 36% after treatment with *R. aquatica* and 62% with *C. wightii*. The IL-6 levels were also reduced in rats[28].

Bhallatak is also a *Rasayana* drug in Ayurveda indicated for degenerative diseases and arthritis. The paradox is that the plant is also classified as *visha dravya* (toxic plant) due to its corrosive properties and needs to be carefully used with close supervision by an experienced clinician. The challenge was to find a temporal window of dose–response, with definite activity and minimal side effects. A novel clinical study design of 'fixed–flexible dosage regimen' was adopted for the clinical study in patients of osteoarthritis[17]. In this study design, the dose escalation was done every week till the study period of 6 weeks, and in case of any adverse event, a provision was made to reduce the dose. The study provided the therapeutic window that helped design a randomized, comparative, long-term study of 6 months[22]. A para-clinical long-term (120 days) animal toxicity study also had a novel component in the design in which one group of animals, receiving traditional therapeutic dose with cow's milk as a vehicle, showed no mortality. The group which received no concomitant milk showed substantial mortality[29].

Another example of a *Shunthi-Guduchi*-based formulation for treating osteoarthritis is notable. The formulation showed improvement in the management of pain and difficulty in knee-joint movements. The same formulation could play a potential role in cartilage protection by reducing its breakdown product (urinary human type II collagen C-telopeptide)[30]. The RP-driven arthritis research demonstrates the case of bio-prospecting Ayurveda concepts to treat a chronic diseases leading to disability and reducing quality of life and productivity of millions of people.

Translational enrichment of traditional medicine

In nations like India and China where there is medical pluralism, questions are often raised by the sceptics about the scientific evidence in Ayurveda and TCM respectively. Tu You You identified the signal from the ancient literature in the form of a 'hit' as a cold aqueous extract of quinhao being useful for malaria. Further, the diethyl ether extract demonstrated anti-malarial activity which gave the 'lead' in isolating active molecule artemisinin[31]. Similarly, the story of active guggulusterone from *C. wightii* vindicated the ancient practice of using *guggulu* for several indications[32]. A large mass of experimental and phytochemical research data exist on the activity of Indian and Chinese plants. But there are adversarial reports on the lack of evidence on safety and efficacy of these plant products in humans. RP can be gainfully applied to generate first-rate, high-impact evidence on the efficacy and safety of Ayurvedic and TCM drugs. A focused intention of RP to translate back to Ayurveda its remedies, with scientific value-addition, can enhance the holistic strength of natural products. RP would have the potential of enriching the domain of integrative medicine.

The opportunities are immense to expedite the entire process from a 'hit' to a 'field application' of a natural drug in a cost-effective manner. Recently, RP has been globally adopted by several workers[33–35]. It is high time that RP is taken up by the academia–industry–Government jointly in a mission mode for the major communicable and non-communicable diseases. There are hits and leads in malaria, dengue, tuberculosis, hepatitis, filariasis, AIDS, arthritis, diabetes, cancer and asthma, even with pilot RP efforts[36]. These hits and leads need to be pursued with vigour and on a war footing. India can truly offer new drugs for arthritis to the world from Ayurveda, within five years with a national RP mission.

Conclusion

Indian scientists should relook at traditional wisdom and adopt innovative research approaches. RP is a transdisciplinary strategy for bridging traditional knowledge-base to the emerging research methods, tools and technologies. RP-based approach in drug discovery can facilitate the long-awaited therapeutic innovations.

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