Special Article

Reverse pharmacological correlates of ayurvedic drug actions*

A.D.B. Vaidya

Bhavan’s Swami Prakashand Ayurvedic Research Center (SPARC), Mumbai – 400 049, India

Received: 28.7.2005
Revised: 22.5.2006
Accepted: 30.5.2006

Correspondence to:
Ashok DB Vaidya
E-mail: bhaspa@bom5.vsnl.net.in

The human condition has been enhanced considerably by those biochemists and pharmacologists who have applied the scientific method to prove ancient myths and legends. For example, the mystical powers of the snake root plant of India, either ignored or ridiculed by scientists for decades, were dispelled with the isolation and identification of its active alkaloid.

– Richard E Davis

Sir Ram Nath Chopra (1882-1973) was a pioneer in the field of experimental pharmacology of indigenous drugs of India. Most of the medicinal plants he studied were in use, in ayurveda, for thousands of years. At the Calcutta School of Tropical Medicine, he pioneered a paradigm, a pace and a pattern of research in studying the actions of medicinal plants, which influenced an entire generation of pharmacologists, pharmacists and physiologists in India. Fortunately, now, at the Regional Research Laboratory (RRL) Jammu-Tawi, the Chopra Archives are safely lodged for posterity. The collected works, correspondence and materials may also serve as valuable sources for a biography which can be commissioned by the Indian National Science Academy, which had the privilege of having Dr. R.N. Chopra as past president. G.V. Satyawati, former Director General, Indian Council of Medical Research (ICMR) has rightly emphasised, “The credit for kindling the interest of Indian chemists and pharmacologists in medicinal plants should rightfully go to Sir Ram Nath Chopra, who has been acclaimed as the ‘Father of Indian Pharmacology’”.[1]

While Sir Ram Nath Chopra and other West-trained scientists were evaluating the effects of ayurvedic drugs and plant extracts on tissues and animals, eminent vaidyas such as Mahamahopadhyaya Gananath Sen were laying the foundation of ‘Reverse Pharmacology’. The science of integrating documented clinical/experiential hits into leads by transdisciplinary exploratory studies, reverse pharmacology further developed these leads into drug candidates by experimental and clinical research. The proposed approach is the new paradigm or a rediscovered paradigm. “Rediscovered” because, even in modern pharmacology, some of the major fundamental discoveries evolved from plant effects in humans. Table 1 lists some such historical examples of reverse pharmacology. The animal models and/or mechanisms of such human effects often provided the foundation of pharmacology. Novel phenomena in healthy or ill humans still continue to occur and deserve a critical study at different levels of biological organisation. This can be an engaging and challenging task. It is possible that such a quest for biodynamic mechanisms can generate new disciplines in life sciences.

Ayurveda in India dates back to 3000 BC. It has a connotation of revealed knowledge, complete within itself and, as some say, it has hardly any need for research. Lokmanya Tilak coined the term ‘Ayurvidya’ to liberate the creative and research energies of this great heritage of healing wisdom. India is a unique, democratic nation with a multi-population, divergent lifestyles and pluralistic healthcare systems. Such diversity offers an immense scope to observe and document the effects of ayurvedic drugs, medicinal plants, dietary habits and non-drug healing modalities. Reverse pharmacology

*Based on the ‘Sir Ram Nath Chopra’ oration delivered by the author at the Annual Conference of the Indian Pharmacological Society on 10th January 2002 in Nagpur.
Table 1
Rediscovery of the paradigm of reverse pharmacology

<table>
<thead>
<tr>
<th>Medicinal plant</th>
<th>Clinical effect</th>
<th>Experimental correlate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curare tomentosum</td>
<td>Paralysis and death</td>
<td>Neurmuscular block[6]</td>
</tr>
<tr>
<td>Papaverum somniferum</td>
<td>Analgesia</td>
<td>Opioid receptors[5]</td>
</tr>
<tr>
<td>Physostigma venenosum</td>
<td>Ordeal poison</td>
<td>Anticholinesterase[4]</td>
</tr>
<tr>
<td>Cinchona officinalis</td>
<td>Antipyrexia</td>
<td>Antimalaria[5]</td>
</tr>
<tr>
<td>Digitalis purpurea</td>
<td>Dropsy relief</td>
<td>Na+ - K+ - ATPase[6]</td>
</tr>
<tr>
<td>Salix alba</td>
<td>Fever and pain relief</td>
<td>Prostaglandins[7]</td>
</tr>
<tr>
<td>Strychnos nuxvomica</td>
<td>CNS stimulant</td>
<td>Glycinergic receptors[8]</td>
</tr>
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would initiate the research process from the robust clinical base of documented therapeutic or other effects of plants and formulations.

As an academic discipline, it comprises 3 phases:
1. Experimental robust documentation of clinical observations of the biodynamic effects of standardised ayurvedic drugs by meticulous record keeping.
2. Exploratory studies for tolerability, drug interactions, dose range finding in ambulant patients of defined subsets of the disease and para-clinical studies in relevant in vitro and in vivo models to evaluate the target activity.
3. Experimental studies, basic and clinical, at several levels of biological organisation, to identify and validate the reverse pharmacological correlate of ayurvedic drug safety and efficacy.

Such a creative research endeavour requires an excellent teamwork by multisystem and multidisciplinary experts. Reverse pharmacology, for drug development, has been highly productive and cost effective in the recent past. Globally, this approach has now generated greater interest in ayurveda and Indian pharmacology.

Rauwolfia serpentina Benth (Sarpagandha)

Sen and Bose[6] not only showed the antihypertensive effects of *R. serpentina*, but were also astute clinicians to note certain side effects such as Parkinsonism, depression, gynecomastia, acid peptic symptoms and so on. There was almost a gap of two decades in discovering the pharmacological basis of these actions. The storage vesicles are rendered dysfunctional as a result of their interaction with reserpine and the depletion of biogenic amines explained the actions by mechanistic correlates.[10] As a spin off of the side effects of *R. serpentina*, several new drugs were developed such as L-dopa, antidepressants, bromo-ergocristine, and H2 receptor blockers and so on.[11-13] The alkaloids of *R. serpentina*, reserpine and ajmaline, have served as research tools in many experiments.[14]

However, there are still some unanswered questions. Does reserpine have more incidence of depression and/or extrapyramidal side effects than the standardised extract of the plant? It is worthwhile to apply combinatorial chemical methods for reserpine derivatives, which do not cross the blood brain barrier, so that depression, a serious side effect, is avoided. The uptake of norepinephrine by isolated chromaffin granules, by inhibition of ATP-Mg++ – dependent mechanism has to be studied afresh at the transcriptional level. Though reserpine is withdrawn globally, the extracts of the plant are still used in ayurveda with a rationale of ayurvedic pharmacodynamics. There is a need to conduct pharmacovigilance on *Sarpagandha ghanavati* (water extract).

Psoralea corylifolia Linn (Bakuchi)

The use of this plant in treating leucoderma is well documented in Rajnighantu (Nighantu – a compendium of synonyms, properties and usages of medicinal plants) by Pandit Narahari.[13] Besides the traditional and classical use of *P. corylifolia* in treating leucoderma (shwitra kusta), there are many other indications described in classic ayurveda texts such as Bhavaprakash Nighantu.[14] These indications include promoting skin health, hair growth, relieving attacks of asthma and bronchitis and reducing inflammatory and edematous conditions. Though the pharmacological correlates of its pigment enhancing and antipsoriasias actions have been studied, the other ayurvedic actions too deserve attention.[17] The phytochemically induced covalent binding of methoxalen to pyrimidine bases is responsible for its therapeutic effect. The photoconjunction involves thymine dimer adducts on the opposite strands of DNA. With the current advances in human genomics, it would be worthwhile to investigate whether such effects on DNA are localised to the skin only and whether hair, retina and so on are also affected. The other ingredients of the plant need to be studied, in the reverse pharmacology mode, for the effects on edema, asthma cough and anaemia. An overt focus on a single active principle leads to the neglect of other active entities in the plant. The external uses described in ayurveda deserve due attention.[18]

Berberis aristata D C (Daruhari)

The multiple uses and actions of the plant, *Berberis aristata* (Daruhari), have always intrigued pharmacologists and clinicians. It is a topical antimicrobial par excellence in ayurveda. Its use, as extract for eye drops in conjunctivitis, is widespread. The active principle of the plant, berberine, has been extensively studied. The activity of berberine against a variety of organisms, including bacteria, viruses, fungi, protozoa, helminths and *chlamydia*, has been demonstrated.[18] Berberine has been shown to bind to DNA and inhibit its cleavage.[20] There is an urgent need to develop specially targeted drug delivery systems of berberine, for topical and systemic antimicrobial use. Local anesthetic, pigment inducing, enzyme inhibitory, antihypertensive, antipruritic and antipyretic activities have been reported with berberine.[21, 22] Recently, the antiamnesic activity of berberine has been reported.[23] Despite the diversity of activities, the proper clinical documentation of the reverse pharmacology of the plant has been neglected. Its beneficial effects on *Plasmodium vivax* relapses have been reported by Gogte.[10] But experiential documentation is urgently needed.
**Picrorrhiza kurroa Royle ex Benth (Kutki)**

Arogyawardhini (a herbo-mineral formulation) was popularized by the late vaidya, Zandu Bhattji, for the treatment of jaundice. A double blind trial with arogyawardhini, kutki and placebo was conducted in viral hepatitis. Significant hepatoprotective effects were observed with kutki, as a single plant or as an ingredient in arogyawardhini.\[24, 25\] Later, picrosides, the active principles of kutki, were also tested in vivo and in vitro. Significant antioxidant as well as hydrocholeteric effects were noted for kutki. These effects of hepatoprotection in carbon tetrachloride (CCL4) and galactosamine models are considered the pharmacological correlates of clinical actions. However, there is a need to study, at the cellular and molecular levels, how the water outflow in the biliary microcanaliculae is enhanced. The Central Drug Research Institute (CDRI), Lucknow, has now developed a cucurbitacin-free extract of *P. kurroa* (Picroliv\[26\]) which has undergone Phase II trials.\[29\] The plant also inhibits passive cutaneous anaphylaxis, as shown by Mahajan.\[37\]

**Commiphora wightii Arnott (Guggulu)**

*Commiphora wightii* (guggulu), which is a major ayurvedic drug, is used widely in diverse formulations. A monograph of all the major citations of its use has been published.\[20\] The hypolipidemic effects of the plant were primarily discovered through the reverse pharmacology mode. Satyavati, Dwarkanath, Sukhdev and Nityanand have extensively studied the hypolipidemic effect of *C. wightii*. The product has been already marketed and widely used.\[29, 36\] However, the antiarthritic effects of *C. wightii* in clinical studies have been relatively less investigated. We have sizeable experimental and pharmacological studies with standardised guggulu preparations. Phase I as well as long term and large dose ambulant studies have been conducted. The ongoing studies at the cellular and molecular levels have helped in evolving pharmacological correlates of clinically shown actions.\[31\] The side effects of the plant have also been documented. The mechanisms of toxicity are yet to be studied. The plant can offer a platform for technological innovations in pharmaceutics, pharmacodynamics and pharmacokinetics. The use of guggulu as a sacrificial incense (homadraya), in sacrificial use (shantikarma), is currently being evaluated for the antimicrobial effects of the volatiles. The topical formulations of the plant demand unique dermato-pharmacological reverse correlates. The different properties of fresh and old gum guggulu, mentioned in ayurveda literature, need additional clinical investigations both experiential and exploratory.

**Tinospora cordifolia Hook (Guduchi)**

In his classic, ‘Indigenous Drugs of India’, Sir RN Chopra wrote, “In spite of the fact that this plant is so extensively used as a household remedy and also by the Tibbi practitioners and much chemical work has been done, the pharmacological action of the active principles isolated has not been worked out. Efforts have not been made to carry out clinical trials with a view to determine its effectiveness in dyspepsia and other conditions”.\[32\] Bapat *et al*, have shown very interesting results with *T. cordifolia* in patients undergoing gall bladder surgery.\[33\] Recently, Chintalwar *et al*, have shown that the polysaccharide fraction of the plant has a mitogenic effect on the B-lymphocytes of the spleen.\[34\]

Clinically, the water extract of *T. cordifolia* has been used to treat pyrexia of unknown origin, frequently, with gratifying results. The pharmacological correlates of the antipyretic actions at the molecular level must be understood ayurveda regards jwara (fever) as a disease entity and not merely as a symptom. Exploring the mechanisms of the jwaraghna (antifever) property of these plants and products such as *T. cordifolia* gives us a totally different perspective on fevers. The use of the plant, as a standardised formulation viz. Immumol\[20\] (Wockhardt Pvt. Ltd.) 500 mg, b.i.d., and after cancer chemotherapy, has led to a reduction in the incidence of nausea, vomiting and granulocytopenia. However, there was no reduction in alopecia.\[36\]

**Curcuma longa Linn (Haridra)**

The wound-healing, anti-inflammatory and antimutagenic activities of turmeric have been demonstrated convincingly.\[17\] However, its cancer preventive action needs to be more actively pursued. Hastak *et al*, have shown its beneficial effect in oral submucous fibrosis – a precancerous condition.\[38\] In dimethyl benzantracene (DMBA)-induced experimental breast cancer, *curcumin* has shown a significant reduction in carcinogenesis.\[39\] These effects are being investigated further by our group. Recently, *curcumin* has been shown to reduce the plaques in Alzheimer’s disease in the animal model.\[40\] It has been stated that Indians have a lesser incidence of Alzheimer’s disease due to a steady and regular consumption of turmeric in their diet. The carminative effect of *curcuma* oil was reported by Sir RN Chopra. He has also referred to a marked diminution of the gastric acid secretion after fractional test meals.\[32\] Hence, it may be worthwhile to study the effects of *curcumin, turmerone*, and so on, on H2 and H1 receptors as well as on the gastric H+K+-ATPase or the proton pump of the parietal cell, by the reverse pharmacology path. Several laboratories have demonstrated the antioxidant activities of *curcumin*.

**Saraca asoca (Roxb) Wild (Ashoka)**

Sir RN Chopra, in his monograph on the *S. asoca* plant, wrote, “This plant drug does not appear to have marked therapeutic effects, though many clinicians appear to vouch for its efficacy in menorrhagia and other uterine disorders”.\[32\] Recently, Shringi *et al*, have shown with a formulation of *S. indica* (Ashotone\[3\]), a reduction in menstrual blood loss, in a distinct subset of menorrhagia, viz., ovulatory dysfunctional uterine bleeding.\[41\] The broad claims of clinical efficacy in ayurveda need to be fine tuned to the subsets of the disease or a syndrome.

**Panchvalkal (Five barks – *Ficus bengalensis, Ficus glomerata, Thespesia populnea, Ficus religiosa, Albizia lebeck*)**

Ranjana Bhatt and her students have shown the burn- and wound healing activity of *panchvalkal*.\[42\] Joshi and colleagues, at Bhavan’s Swami Prakashanand Ayurvedic Research Center (SPARC), have shown some significant efficacy in leucorrhoae.\[43\] A standardised novel formulation of *panchvalkal* has already been developed by Viridis

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**Reverse pharmacology**

Indian J Pharmcol | October 2006 | Vol 38 | Issue 5 | 311-315
Bio-pharma and clinical trials have shown its remarkable wound healing activity. A further investigation into the mechanisms of wound/burn healing by *panchwalkal* is needed. The activity of *panchwalkal* against resistant microbes *in vitro* offers unique advantages which need to be pursued clinically.

**Azadirachta indica A. Juss (Neem)**

The plant is a major medicinal tree of common household use in India. It has currently drawn international attention as an antifeedant for pests and due to the patent battle on one of its active principles, azadirachtin. Sir KN Chopra cites the study conducted by Chatterjee with sodium margosate in treating syphilis patients. The results, though positive, were not comparable to the organometallic compounds. But now there is a need to explore the use of sodium margosate in treating Lyme disease *in vitro* and *in vivo* animal studies should precede clinical dose searching in Lyme disease.

In 1925, Chatterji successfully used a copper margosate-ester in patients with head and neck cancer. This needs a careful re-evaluation in the reverse pharmacology mode. Head and neck cancer constitutes a major problem in India. Hence, any potentially complementary therapy is worth exploring in those patients, where it could enhance the quality of their lives.

Neem has shown antiviral activity against tobacco mosaic virus, human papilloma virus and varicella (clinically). However, the effects of diverse preparations of *A. indica* in treating HbsAg (Hepatitis B surface antigen) carriers, HIV-infection, *Chlamydia trachomatis* and so on, in humans, have not been investigated adequately. Reverse pharmacology can help in expediting such studies in a cost effective manner by a network research and development. The activity of neem in treating malaria also needs to be pursued.

**Therapeutic revolution through reverse pharmacology**

Finally, one would like to re-emphasize that the pluralistic healthcare system of India offers a virtual gold mine for novel clinical observations, beneficial or adverse. A scientific analysis of the *de novo* actions of natural products suggest a need for the reverse pharmacology approach in the development of safe, effective and acceptable therapeutic agents. There is a need to create educational modules for such an approach. Pharmacologists and clinicians need to work in tandem for this novel route to drug development, new uses of old drugs, more effective and safe derivatives of active plant principles, new drug delivery and novel bioenhancers of plant origin.

Indian contributions by reverse pharmacology to therapeutic revolution will have to eventually integrate state of the art high throughput screening, combinatorial chemistry and effects of the old or novel compounds/plants on human gene expression and proteomics. Sir Gananath Sen, Sir KN Chopra, Dr. Rustom Jal Vakil and other doyens of Indian reverse pharmacology will then be vindicated. It is my appeal to the young generations, working in life sciences and molecular pharmacology, to take up this challenge and put India back on the world map of therapeutic discoveries.

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National Seminar on Drug Standardisation in Ayurveda 2006

Date : November 6th & 7th , 2006

Place : Rajeev Gandhi Centre for Biotechnology, Jagathy,
Thiruvananthapuram, Kerala

Contact address:

Dr. A. Thankamma
General Convenor, NSDSA
Drug Standardisation Unit,
Govt. Ayurveda College,
Thiruvananthapuram – 695 001. Kerala
Phone: 91-94475 53292