Drug discovery from plants

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In their recent article in *Current Science*, Jachak and Saklani[1] have not cited the article on ayurveda and natural products drug discovery[2], which has relevance to the subject. They have also not touched upon the earlier researches on Indian medicinal plants.

Investigations on Indian medicinal plants had been going on since the 1930s, having been initiated by R. N. Chopra. The discovery of reserpine (serpasil) from *Rauwolfia serpentina* by Ciba in Switzerland in 1952, gave a new impetus to research on herbal drugs in India.

Although we had special strengths in the investigation of plant products, our record is rather unimpressive. Peruvoside[3] from *Thevetia neriifolia* (syn. *T. peruviana*) seems to be the only plant-derived new compound to be used in medicine, although, ironically, not in India. The CSIR patent[4] and the pharmacological report from CDRI, Lucknow[5] on the possible use of peruvoside as a cardiotonic drug did not evoke much interest in India. E. Merck, Germany, carried out detailed pharmacological studies followed by extensive clinical trials for treating cardiac insufficiency[6]. However, they have not commercialized it.

The German scientists' work was readily exploited by an Italian firm, Inverni della Beffa (IdB), which specializes in the manufacture of pure natural product drugs. Simes, an Italian pharmaceutical company, manufacturers the dosage forms of peruvoside for marketing under the proprietary name *nerial*[7] for use in Italy and other European countries. China also utilized the German studies and carried out clinical trials on neriperside[8] (a mixture of peruvoside, neriifolin and cerberin, all constituents of *T. neriifolia*[3]) for the treatment of congestive heart failure.

In the wake of international interest in reserpine and peruvoside, ICMR had given specific research projects on medicinal plants in 1970s, to researchers of organic chemistry in India, but no new chemical entity (NCE) with interesting pharmacological activity came out of these projects. Investigations on Indian herbs were vigorously pursued in CSIR laboratories, Ciba Research Centre, Hoechst Research Centre, etc. involving the screening of thousands of plant extracts. No NCE had been commercially introduced. However, two products need special mention: forskolin (coleonol) from *Coleus forskholii* (Hoechst and CDRI), and gugulipid from *Commiphora mukul* (CDRI).

Forskolin, a diterpenoid of the labdane-type, is a major discovery because of its inotropic and antihypertensive action mediated through stimulation of adenylate cyclase. Unfortunately it failed at the phase III clinical trials. Several forskolin analogues with potential for drug use have been developed in India[9]. Among these, NKH 477 is a water-soluble derivative which has undergone clinical trials as a cardiotonic in Japan. HIL 568 reduces the intraocular pressure of rabbits and was developed for the treatment of glaucoma. Brown University (USA), Hoechst, and Nippon Kayaku manufacture these drugs.

Gugulipid, a standardized extract from *Commiphora mukul*, containing guggulsterones (*Z* and *E*) as the active principles was developed by CSIR and is commercially available both in India and Europe for use as a hypolipidaemic agent. According to a study made at the University of Pennsylvania, USA[10], 'guggul resin' might have dangerous effects on cholesterol levels. The report mentions that differences in genetics, diet or both might explain why it did not work in their study. However, what was not clear is whether the study made use of the standardized extract or guggul resin as sold in the market. Either way, use of pure active principles may obviate the problem.

Picroliv (RRL, Jammu) is again a standardized extract containing kutkin (mixture of iridoid glycosides, kutkoside and picroside-I) found in *Picrorhiza kurroa*[11]. It was reportedly undergoing clinical trials as a hepatoprotective agent. The only known hepatoprotective pure chemical entity is the favanolignan silymarin (silybin) isolated from *Silybium marianum* in Germany[12]. A later development was the silybin phosphatidylcholine complex (silipride, IdB-1016)[13], with increased bioavailability to the liver. It will be of interest to compare picroliv with silybin/silipride.

No NCE with proven clinical application had come out from any of the top 20 ayurvedic drugs listed by Patwardhan *et al.*[2]. Use of well-known plant products for commercial application after clinical trials has not succeeded, e.g. vasicine as oxytocic (antifertility agent; by RRL, Jammu) and curcumin as anti-inflammatory agent (CDRI). Compounds from reputed herbal drugs like jatamansone from *Nardostachys jatamansi* (tranquillizer) and shatavarins from *Asperagus racemosus* (for duodenal ulcer) have not been shown to be clinically useful. Many claims of activity of medicinal plants could not be verified, including the well-known one for the antidiabetic property of bitter-gourd juice[14].

Thus challenges for drug discovery from Indian medicinal plants are many, but opportunities are not easy to come by as far as NCEs with clinical usefulness are concerned. However, the discovery of new plant-derived drugs by the renewed efforts of CSIR and industry research centres will contribute to the health-care needs of the nation.

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