

INDUSTRY - INSTITUTION LINKAGE FOR DEVELOPMENT OF HERBAL PHARMACEUTICALS

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Synthetic processes for which a chemist requires enormously high degrees of heat & pressure are quietly carried out by nature in plant cells at ordinary conditions of temperature & pressure. For example, chemists could synthesize such alkaloids as quinine after intensive work extending over half a century whereas cinchona plant does this without any difficulty every day. Many active antibiotics, anti-cancer drugs and other therapeutic substances are present in plants and this is yet an unexploited field.

History shows that many herbs were in use long before they were introduced in modern medicine. During 1970s to 1990s, 25% to 30% of all drugs dispensed in USA contained compounds of plant origin and their worldwide contribution was more than 48%. Today, 15% of the basic and essential 257 drugs (WHO) are of flowering plant origin. A recent survey found that 477 out of 868 drug molecules discovered during 1981 to 2002 belonged to natural products. In 2000 alone, seven out of twenty best-selling non-protein drugs including statins, enalapril, amoxicillin etc were derived from natural products.

Herbal preparations have been in use in India, since ages for improving health and production of animals. For example, during Mahabharat war (1000-900 BC), the Pandav Prince Nukul and Sahdev used to treat thousands of wounded and diseased animals everyday with herbs as described in the book Nakul Samhita. Salihotra (700 BC), wrote Asva-Chikitsa in Sanskrit, dealing with equine husbandry and herbal medical care. Ayurveda (2500 B.C.) gives account of ancient medical science of India, which includes the use of herbs.

Modern medicine was thought to be able to solve almost all health problems of humans and animals, but this overestimation changed in the course of the 'green wave', characterised by an increasing demand for natural products in the form of foods, drugs and cosmetics. It was mainly triggered by the side effects resulting from the increasing use of synthetic chemical products and reconsideration was initiated by WHO in the 1970s.

Now the research on use of herbs for better health and production performance of animals is also gaining importance, because antibiotic growth promoters and other chemical treatments of synthetic origin are being restricted due to resistance development, residue problems and other human health issues.

The thought published in an eminent journal on practical medicine THE PRACTITIONER, December, 1950, is still valid which states that "*The lore of the countrymen is built upon the experience of generations, often of centuries and the data upon which it is based have often been obtained at a price in human lives which no modern research worker would ever dream of considering. It is particularly appropriate at the present moment, when pharmaceutical companies of*

the world are emitting an unceasing flow of new synthetic drugs, that attention should be turned to the possible remedies that may be found among indigenous herbs of this and other countries."

The same applies to use of herbs for animal health care.

Herbal R&D

Research on herbs for development of animal health care products may be initially focused in the following areas :

- (i) Selection of herbal ingredients.
- (ii) Scientific validation of their efficacy and safety.
- (ii) Identification of the active constituents (biomarkers), analytical development and determination of the specification limits.
- (iii) Development of formulations and clinical trials.

Selection of Herbs

For development of a particular therapeutic agent, the herbs may be selected on the basis of their use described in the traditional literature and modern research findings. They may then be subjected to pharmacological screening to re-validate their biological activities. The herbs exhibiting potent biological activity may be subjected to toxicological studies (LD50, acute, sub-acute, chronic, teratological toxicity etc). The herbs showing potent biological activity along with high safety profile may thus be selected for further research. Combination of herbs may be used to enhance therapeutic response with their synergistic effect and to minimize the side effects, if any.

Dose Determination

The optimum therapeutic dose may be established from the dose-response curve by classical pharmacological techniques and further confirmed in clinical trials. In case of extract, the dose should be calculated considering the extractive value of the particular extract from the herb.

Identification and Quantification of Active Substances

The bioactive principles in herbs may be identified through bioactivity guided fractionation assay. Herb is successively extracted with solvents of increasing polarity and the different solvent extractives are subjected to biological screening. The bioactive extractives are further fractionated to separate the individual chemical constituents by using chromatographic and molecular sieving techniques. The isolated individual chemical constituents may be subjected to biological screening to identify the biomarker(s) of the each herb. The structure of the biomarker may be established by studying the physical and chemical properties and using NMR, IR, Mass Spectroscopy, UV-Spectroscopy etc.

Analytical Protocols

Analytical protocols to quantify the biomarker(s) in the individual herbs or their extracts are then developed using the state-of-the-art instruments like HPTLC, HPLC, GCMS, LC-MS, UV

Spectrophotometers etc. The specification limit is assigned considering the results of the locational and seasonal variation studies. The developed formulations are subjected to stability screening by conducting accelerated stability studies at elevated temperatures and humidity and also in normal storage conditions. Specifications are then developed for physical and chemical parameters. Microbiological, pesticide and heavy metal testings are done to ensure that they are within the prescribed limits.

Formulation Development

The selection of right herbs and development of herbal formulations is a unique combination of art and science, where knowledge and experience play an important role. The selected bioactive and safe herbs or extracts are formulated into a suitable dosage form such as powders, liquids, tablets, capsules, ointments etc. Generally where a single herb can not fully serve the purpose, synergistically active herbs are selected for development of formulation.

Experimental and Clinical Studies

The developed formulations are subjected to clinical trials in experimentally induced conditions and in field conditions to assess the efficacy, toxicity and safety profile, in comparison to untreated control group and/or against a group treated with a known synthetic drug currently in use in the same segment.

The results of these trials provide information about the level of efficacy and safety profile of the developed product.

In the modern age, chemical drug discovery is the process whereby chemical compounds with activity against a specified target or function are identified, evaluated and optimized for clinical application. Herbal drug discovery follows a different approach. Herbal drug development starts with collection of data on raw materials, correct identification of herbs, pharmacognostic and quality standardization, safety and pre-clinical pharmacology and proceeding to clinical pharmacology and controlled clinical trials.

Patenting, pharmacosurveillance, formulation development, quality control of finished product, packaging and marketing follow them. In the sequence of their appearance, the scientific disciplines involved in herbal drug discovery are pharmacognosy, botany, phytochemistry, physiology, pharmacology, medicine, microbiology, biochemistry and molecular biology etc.

So there is a vast opportunity for multidisciplinary approach for successful herbal drug research with involvement of the experts from the fields of medicinal and phytochemistry, molecular and cellular biology, synthetic and analytical chemistry, pharmacology and medicine, regulatory affairs, information technology and pharmaceuticals. None of the components are less important than the others.

The conventional approach in seeking out new chemical drugs involves identifying new molecules, testing their efficacy on laboratory animals, and then moving to humans.

Chemical drug discovery around the world has focused on moving drugs from molecules to mice to men. 'Reverse Pharmacology' is the alternative and most suitable approach for efficient

discovery (re-discovery!!) of herbal drugs with very few bottlenecks. In reverse pharmacology we are going the other way – from men to mice to men. Traditional herbal medicine has long been used in clinical practice. Reverse pharmacology is aimed at validating such herbal drugs through modern scientific methods.

Academia has the expertise in many of the above fields such as pharmacognosy, pharmacology, toxicology and therapeutic evaluation and they come into direct contact with patients for pre-clinical and clinical drug trial.

It is known that academic organizations are fully competent in target identification, lead identification, lead optimization, ethical clearance, pre-clinical efficacy and safety trial and controlled clinical trials etc, while the industries have the expertise in raw material identification and collection, standardization, extraction and quantification of active molecules, quality control, formulation development, patenting & regulatory affairs and pharmacosurveillance etc.

Therefore for herbal drug discovery programme, if linkages are established between industry and academia, there would be ample opportunities for development of numerous effective therapeutic agents. Now Govt. of India, through DST and DBT, is financially supporting development of herbal medicines for animal health care. Indian Herbs, Saharanpur has long been associated with herbal drug development in its highly modernised and sophisticated R&D Centre and open to joining hands with academic institution and universities.

We have been associated with academia for herbal drug development for animal and human health care since 1960s. Indian Herbs sponsored first PG research on herbal drugs in the year 1968 and since then many research studies have been conducted in almost all Veterinary Colleges and Agriculture Universities in India and I.V.R.I., C.A.R.I., N.D.R.I. etc. We have so far sponsored as many as 176 post-graduate and doctorate research studies in different veterinary academic institutes for herbal drug development. During last few years, we had collaboration with various departments of this University (CSK-HPKV, Palampur), for evaluation and development of some herbal animal health care products like FerroCom, ART, Dermanol, BioCholine, Himax etc.

Let us now make a new beginning with greater commitment and close linkage at higher level for development of herbal pharmaceuticals, needed for our livestock, poultry, pets and other animals as well as human beings.