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Prospects, Problems & Approaches To Alternative System Of Medicine: A Review

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There is a trend for synthetics to replace natural compounds in Prescription and Over the Counter (OTC) Pharmaceuticals. Today, ephedrine, salicylates, vitamins, and xanthines are mostly synthetic and steroids are often semi synthetic. While agreeing with Farnsworth and Bingel (1977) that 25% of modern prescription drugs contain at least one phytochemical, I suspect that only about 10% of our leading drugs (excluding the illicit drugs, cocaine, crack, hashish, heroin, marijuana, and opium) now contain phytochemicals still extracted directly from the higher plants. Due to their long historical clinical use and reliable therapeutic efficacy, traditional Indian medicine attract and increase global attention, and many big pharmaceutical companies are using traditional Indian medicine as an excellent pool for discovering natural bioactive compounds. If only few constituents are emphasized, the holistic nature will be neglected, which needs to be studied and scientifically understood. With the growing need for safer drugs, attention has been drawn to their quality, efficacy and standards of the traditional Indian medicine formulations.

COST & TIME FACTORS

American consumers want natural drugs, believing natural drugs are safer than synthetics. The pharmaceutical firms seem to prefer synthetics or semisynthetics, in part due to proprietary economic reasons. The health of the drug company by necessity must concern the drug company before the health of the consumer. As noted in a International Trade Commission Study, "Between 1976 and 1990, *the cost of developing a pharmaceutical product in the US increased from $54 million to $231 million*. Only one out of every 4,000-10,000 compounds discovered can be marketed commercially--after which a company has less than ten years to partially recoup its R&D investment before its patent expires and generic manufacturers enter the market or a me-too drug is created by a competitor" (Chemical Marketing Reporter 1991). Such investments may lead pharmaceutical firms to prefer a proprietary synthetic or semisynthetic to a relatively less proprietary herbal or natural product.

ECOLOGICAL AND ENVIRONMENTAL FACTORS

India is one of the 12 mega biodiversity centres having 45, 000 plant species; its diversity is unmatched due to the 16 different agroclaimatic zones, 10 vegetative zones, and 15 biotic provinces. The country has a rich floral diversity (Table 1).

Table 1: Floral diversity in India.

Numbers	Species
15, 000 - 18, 000	Flowering plants
23, 000	Fungi
25, 000	Algae
1,600	Lichens
1,800	Bryophytes
30 million	Microorganisms

Traditional medicine is the synthesis of therapeutic experience of generations of practicing physicians of indigenous systems of medicine. Traditional preparation comprises medicinal plants, minerals and organic matters etc. Herbal drug constitutes only those traditional medicines that primarily use medicinal plant preparations for therapy.

A major problem with traditional, indigenous medicine is discovering a reliable 'living tradition' rather than relying upon second-hand accounts of their value and use. In many parts of the world the indigenous systems of medicine have almost completely broken down and disappeared. This includes mostly developed countries and some developing countries where the indigenous population has been marginalized. In others, the system is fragmented with the use of indigenous materials being limited to small tribal and geographical areas, as in many parts of Africa. In anthropological terms these are 'little traditions', while the Ayurvedic Indian and traditional Chinese systems are living 'great traditions'. Although the little traditions are an excellent repository of knowledge about medicinal and poisonous properties of botanicals, researchers have mainly exploited poisonous sources. This may be primarily because of many reasons. First, it is relatively easy to present and demonstrate poisonous characteristics of botanicals. Second, there may not be a written documentation and poisonous characters get predominance by word of mouth. Third, for an outsider, poisonous characteristics differentiate between ordinary and extraordinary material for pharmaceutical development. Fourth, a considerable time period is required to demonstrate true medicinal activities with proven safety profile. Great traditions have relatively organized database, and more exhaustive description of botanical material is available that can be tested using modern scientific methods. Ayurveda and Chinese medical systems thus have an important role in bioprospecting of new medicines. Little or poor knowledge about these ancient systems of medicines leads to encourage the manufacturers to go for investigating in Synthetic drug discovery.

Environmental factors as a whole creates a lot of problem in cultivation of the plant drugs resulting in poor availability of the plant drugs for manufacture of formulations on a commercial basis, which leads to biasness of the manufacturers towards the Synthetic or Semi synthetic drugs.

EXTRACTION, ISOLATION AND CHARACTERISATION

Indigenous peoples derived medicines and poisons from thousands of plants. A review of some plants that originated from Central and South America indicates that most of them either had potentially toxic characters or were from food sources. The following are a few examples2: In the early 1500s, Indian fever bark was one of the first medicinal plants to find appreciative consumers in Europe. Taken from the cinchona tree (*Cinchona officinalis*), the bark was used as an infusion by native people of the Andes and Amazon highlands to treat fevers. Jesuit missionaries brought the bark back to Europe. By the early sixteenth century, this medicine was known as 'Jesuit fever bark', quite a transformation. The name coca (*Erythroxylum coca*) comes from an Aymara word meaning 'tree'. In Andean cultures, the leaves of the coca tree have been primarily chewed to obtain perceived benefits. From ancient times, indigenous people have added alkaline materials such as crushed seashells or burnt plant ashes to the leaves in order to accentuate the pharmacologically active moiety of coca. In 1860, a German chemist Carl Koler isolated cocaine, the chemical responsible for the biological activity. He found that cocaine could act as a local anaesthetic in eye surgery. As the years passed, scientists observed that cocaine paralyzed nerve endings responsible for transmitting pain. As a local anaesthetic, it revolutionized several surgical and dental procedures. Pot curare arrowhead poison used in the East Amazon is predominately from the species *Strychnos guianensis*. Tube curare in the West Amazon is from *Chrondrodendron tomentosum*; curare in modern medicine is made from this and named as tubocurarine. The jaborandi tree (*Pilocarpus jaborandi*) secretes alkaloid- rich oil. Several substances are extracted from this aromatic oil, including the alkaloid pilocarpine, a weapon against the blinding disease, glaucoma. American Indians on the island of Guadeloupe used pineapple (*Ananas comosos*) poultices to reduce inflammation in wounds and other skin injuries, to aid digestion and to cure stomachache. In 1891, an enzyme that broke down proteins (bromelain) was isolated from the fresh juice of pineapple and was found to break down blood clots. Other pharmaceuticals that have their origin in botanicals include atropine, hyoscine, digoxin, colchicine and emetine. Reserpine, an anti-hypertensive alkaloid (*Rauwolfia serpentina*) became available as a result of

work carried out by Ciba-Geigy in India. It is pertinent to note that most of these early discoveries are mainly based on traditional medicines; many products could act as poisons in toxic doses.
Thus, we come to know that in earlier days also Crude Drugs were used as Extracts in one or the other way. And till date extraction in large scale is a tiering and hectic work. Specially skilled workers with special training are needed for this purpose. Solvents to be used are also to be identified by trial and error method. Solvents moreover are costly, except for Water. So, it is also one of the problem for Herbal drug Discovery.
Identification of the marker compound is difficult in herbal formulation due to large no. of phytoconstituent present in them. For this the complexity in separation occurs. Certain phytoconstituents are found to be present in complex form. This also poses problem in isolation and separation of the marker compound or the active component. More over identification and isolation of the phytoconstituents need use of more advanced and sophisticated instruments and processes, which render them costly, while going for large scale manufacture of formulations involving phytoconstituents which can't be synthesized chemically.

RAW MATERIALS

In Formulations involving Herbal Drugs, one of the biggest disadvantage is the irregular supply of Raw Materials & Raw materials from different regions collected separately, but supplied in a bulk, this leads to varying % of active constituents in crude drugs of a bulk supplied. Sometimes adultration with substandard varieties also leads to poor quality of finished products, adultrants are used to reduce the cost to the suppliers and to meet the demand of the market.

The amount of constituents in plants ranges from 0.01-15%. Certain plant contains very very less amount of constituent. For example taxol obtain from bark of Taxus bravifolia requires three mature 100-years old trees to provide 1 gm of taxol, but the course treatment may need 2gm of taxol. For these reasons the Pharmaceutical Industries goes for production of synthetic and semi synthetic drug.

BIOCHEMICAL SCREENING

Once the botanical identity of a herb is established, the next step in drug research is Phytochemical / Biochemical screening, which involves bioassays, extraction, purification and characterization of the active constituents of Pharmaceutical importance. The herb or herbal drug preparation in its entirety is regarded as the active substance. These constituents are of known therapeutic activity. In any work where the end product is to be a drug, some type of pharmacological screening or evaluation, obviously must be done.The ideal pharmacological screening would be to identify those extracts or pure compounds that are highly active and non toxic. Such a screen is rare to find and failure to duplicate Pharmacological results is another problem.There are many Pharmacological screening tests available. In random selection process, plants are randomly selected, extracted and the extracts are evaluated against one or more in-vitro and in-vivo tests. An extension of this procedure is to isolate metabolites or active compounds from plants showing promising activity and subject them to Pharmacological tests again. In another approach, plants containing specific types or class of chemical compounds say alkaloids are tested.Another method involves random collection of plants and subjection of their extracts to several broad screening methods and pharmacological tests. The success of this method depends on the number of samples assayed, adequate funding and appropriate predictable bioassay protocols.The technology of herbal medicinal screening process has even advanced to enzyme isolation. The enzymes that cause the disease are first isolated and the plant extracts are tested to determine if they can block the enzyme action.

CLINICAL TRAILS

Maximum problem occur during Clinical trials, because the practitioner does not give a single formulation to the patients. For which the efficacy can't be conform for that plant formulation. Very less company gives attention towards its clinical trail and also for standardization. The basis of traditional medicine is in its use for a number of years and therefore its clinical existence comes as a presumption. However, for bringing more objectivity and also to confirm traditional claims, systematic clinical trials are necessary. In Ayurvedic medicine research, clinical experiences, observations or available data becomes a starting point. In

conventional drug research, it comes at the end. Thus, the drug discovery based on ayurveda follows a 'reverse pharmacology' path. Nevertheless, all the critical pharmacopoeial tests such as dissolution time, microbial, pesticide and heavy metals contamination, etc. must be in accordance with global standards.

ASSESMENT OF QUALITY

Quality control for the efficacy and safety of herbal products is essential. The quality control of phytopharmaceuticals may be defined as the status of a drug which is determined either by identity, purity, content and other chemical, physical or biological properties or by the manufacturing process. Compared with Synthetic drugs, the criteria and the approach for herbal drugs are much more complex.

Accounting to WHO it is the process involving the physicochemical evaluation of crude drug covering the aspects, as selection and handling of crude material, safety, efficacy and stability assessment of finished product, documentation of safety and risk based on experience, provision of product information to consumer and product promotion.

Macro and Microscopic Examination: For Identification of right variety and search of adulterants.

Foreign Organic Matter: Remove of matter other than source plant to get the drug in pure form.

Ash Values: It is criteria to judge the identity and purity of crude drug – Total ash, sulfated ash, water soluble ash and acid insoluble ash etc.

Moisture Content: To check moisture content helps prevent degradation of product.

Extractive Values: These are indicating the approximate measure of chemical constituents of crude drug.

Crude Fiber: To determine excessive woody material Criteria for judging purity.

Qualitative Chemical Evaluation: It covers identification and characterization of crude drug with respect to phytochemicals Constituent.

Chromatographic Examination: Include identification of crude drug based on use of major chemical constituent as marker.

Qualitative Chemical Evaluation: Criteria to estimate amount the major class of constituents.

Toxicological Studies: Pesticide residue, potentially toxic elements, and Microbial count approach to minimize their effect in final product.

Phytopharmaceuticals are always mixtures of many constituents and are therefore very variable and difficult to characterize. The active principle(s) in phytopharmaceuticals are not always known. The quality criteria for herbal drugs are based on a clear scientific definition of the raw material. Depending on the type of preparation, morphological property, physical constants, moisture, ash value, solvent residues and adulterations have to be checked to prove identity and purity. Microbiological contamination and foreign materials, such as heavy metals, pesticide residues, aflatoxins and radioactivity, also need to be tested for. To prove the constant composition of Herbal preparations, appropriate analytical methods have to be applied and different concepts have to be used in order to establish relevant criteria for uniformity.

The International Conference of Drug Regulatory Authorities (ICDRA) at its 9^{th}, 10^{th} and 11^{th} meetings and the meeting of the National Centers Participating in the WHO Drug Monitoring Programme requested WHO to develop and constantly update the Technical Guidelines on quality, safety and efficacy of Herbal medicines.The participants at the WHO informal meeting on methodologies for quality control of finished Herbal products, held in Ottawa, Canada on 20-21 July 2001, also reviewed the entire production process of Herbal medicines, from Raw materials to Distribution and Supply of finished Herbal products. Recommendations from this meeting led to the development of the General Guidelines addressing the important issue of safety and quality of Herbal medicines with special reference to contaminants and residues.

<u>WHO Guidelines for Quality Standardized Herbal formulations</u>

Standardization and quality control parameters for herbal formulations are based on following fundamental parameters:

1. Quality control of crude drugs material, plant preparations and finished products.
2. Stability assessment and shelf life.

3. Safety assessment; documentation of safety based on experience or toxicological studies.
4. Assessment of efficacy by ethnomedical information and biological activity evaluations.

MODERN ANALYTICAL TOOL

Multi-component botanical formulations can be standardized with newer techniques such as DNA fingerprinting, High pressure thin layer chromatography (HPTLC), liquid chromatography–mass spectroscopy. In-house monographs need to be evolved and critically followed. For example, a multi-component botanical formulation designed for the treatment of arthritis contains four botanicals and all ingredients, their respective extracts and the formulation are standardized using HPLC and HPTLC fingerprint profiles with known markers. Preclinical studies on ayurvedic medicines are more important for validating drug safety resulting from new procedures, or extractions are used during its preparation. The value of animal testing to establish safety and toxicity is not so critical if the botanicals are used in traditional forms. Suitable animal models help in understanding the mechanism of action or pharmacodynamics of medicines. However, it is well known that no good animal models exist for some human diseases; for example, asthma, diabetes and rheumatism.

Chromatography

In general, chromatography involves moving a solution of the mixture to be separated or the "test sample" over a stationary support. The molecules in the test sample will have different interactions with the stationary support leading to separation of similar molecules. Test molecules which display tighter interactions with the support will tend to move more slowly through the support than those molecules with weaker interactions. In this way, different types of molecules can be separated from each other as they move over the support material. Chromatographic separations can be carried out using a variety of supports, including immobilized silica on glass plates (thin layer chromatography), very sensitive High Performance Thin Layer Chromatography (HPTLC), volatile gases (gas chromatography), paper (paper chromatography), and liquids which may incorporate hydrophilic, insoluble molecules (liquid chromatography).

Purity Determination

Each monograph includes standards of purity and other qualitative assessments which include when appropriate: foreign matter, ash, acid-insoluble ash, moisture content, loss of moisture on drying, and extractives.

High performance thin layer chromatography (HPTLC) is valuable quality assessment tool for the evaluation of botanical materials. It allows for the analysis of a broad number of compounds both efficiently and cost effectively. Additionally, numerous samples can be run in a single analysis thereby dramatically reducing analytical time. With HPTLC, the same analysis can be viewed sing different wavelengths of light thereby providing a more complete profile of the plant than is typically observed with more specific types of analyses.

CONCLUSION

Herbal drug standardization is massively wide and deep. Quality control of herbal medicines has not only to establish reasonable analytical methods for analyzing the active constituents in herbal medicines, but many other factors should be concerned, such as pesticides residue, aflatoxine content, the heavy metals contamination, good agricultural practice (GAP), good manufacturing practice (GMP), etc. There is need for development of techniques which includes both traditional methods of evaluation and modern methods of evaluation. This will improve the quality of the drug and also motivates the practitioners to get more involved in the standardization process.Overcoming the various problems, the vast knowledge of the important herbs found in India and widely used in Ayurvedic formulation should be explored in collaboration with the new standardization techniques. Advancement on this path will help us authenticate quality of traditionally important herbs thereby reducing further problems. Quality if ensured at the starting point will eliminate all problems in quality control of herbal formulations to obtain better formulations.

Moreover the society will be benefitted with safer drugs at affordable price, leading to the Goal of WHO "Health for All".

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