INTEGRATION OF INDIAN TRADITIONAL HERBAL MEDICINES WITH MODERN TECHNOLOGIES - AN OVERVIEW

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Summary

The booming of traditional medicine industries in India results an increasing demand on medicinal plants. Being chemically diverse they are able to modulate several targets simultaneously in a complex system. Analysis of gene expression by using modern technologies like genomics and proteomics becomes necessary for the better understanding of molecular mechanisms. Conventional strategies for gene expression have been optimized for single gene expression. Besides, DNA microarray and 2D gel electrophoresis serves as suitable high throughput tools for simultaneous analysis of multiple genes. This review highlights the applications of modern technologies for the development of traditional medicines research in India.

Introduction

Plants occupy a unique position in this planet since they are the foundation to life on the earth. They are the primary producers in all food chains. Plants directly supply 90% of human calorific intake and 80% of proteins intake. Plants are being used as a potential source of medicine for time immemorial. In India, 80% of the populations reside in small and often remote villages where per capita income is very meager and cannot afford the expensive modern medicines. India is the source of wealth of a large number of medicinal herbs and they are opting for the traditional medicine methods. Hence, it is imperative that this great natural resource is augmented and utilized in accordance with the development of technology and the needs of human beings.

The current millennium sets the goal of side effect free treatment by way of nutraceuticals. The global interest on traditional medicine has gained importance as a number of plants have been cited in curing diseases successfully. Medicinal plants are an integral part of the ethnobotanical aspects of the people of Asia for centuries. The modern medicine has evolved from folk medicine and traditional system only after thorough chemical and pharmaceutical screening. Advanced microbial and chemical methods can synthesize medicinal and aromatic compounds, but the cost in many cases is expensive. Nevertheless, the use of synthetic compounds leads to a decline in the use of plants in modern medicine. However, synthetic medicine can cause side effects and as a result, people are more favourable to use natural compounds obtained from plants. Penos[1] estimated that 20,000 plant species are used for medicinal purposes. Farnsworth *et al*.[2] recorded that 74% of 119 plant derived drugs were discovered as a result of chemical studies to isolate the active substances responsible for their traditional use.

The Asiatic flora includes tropical, subtropical and temperate species, which provide systems for herbal based drugs and these systems play a major role in overall healthcare. Farnsworth *et al*.[2] has reported that more than 80% of people in Asia are still depending on traditional and folk remedies for day-to-day medical needs. More than 70% of India's 1.1 billion populations still use the traditional herbal medicine[3]. Scragg[4] has reported the use of phytochemical analysis of plants, used in folklore for the treatment of cancer, yielding a number of compounds with antitumour activity. Plants from many families have shown to accumulate alkaloids, which possess anti-HIV activity. Hussein[5] reported several plant-derived drugs and aromatic compounds. These include anti-malarial agent from *Artemisia annua*, forskolin from roots of *Coleus*, which is used for preventing the clotting of blood in reducing intraocular pressure in cases of glaucoma. Forskolin also acts as an aid to nerve regeneration following trauma.

The medicinally active organosulfur compounds of garlic and onions are also useful cardiovascular agents, while ellagic acid is tested for its possible utility as a prototype anti-mutagen and cancer-preventing agent. Other bioactive compounds discovered and commercially used in Europe and Japan are herandulcin, an intensely sweet sesquiterpenoid, stevioside and glycorrhizin. The development of bioassay techniques for the isolation of bioactive natural products should provide the means of identifying new plant-derived antiviral, antitumour, immunostimulating and adaptogenic agents. Asiatic ginseng is just one of the many species used for investigation as potential adaptogenic crude drug. Plants have been used in the treatment of cancer for over 3500 years[6]. But it is only since 1959 that a concentrated systematic effort has been made to screen crude plant extracts for their inhibitory activity against tumour systems. Under the programme sponsored by the National Cancer Institute (NCI), USA, around 2, 00,000 plant extracts from 2,500 genera of plants have been screened[7].

Traditional medicines in India

In India about 7,300 plant species are used in traditional health care systems such as Ayurveda, Siddha, Unani and folk healing practices. The booming of traditional medicine industry results in an increasing demand on medicinal plant products. 90% of the medicinal plants come from natural habitats. The declining availability of such plants and the fading of local traditional knowledge make the sustainable management of natural habitats a crucial environmental issue in South India, concerning biodiversity conservation and welfare of local communities.

Recognization of Herbal Drugs in India

India has a very long, safe and continuous usage of many herbal drugs in the officially recognized alternative systems of health viz. Ayurveda, Yoga, Unani, Siddha, Homeopathy and Naturopathy. The industry, the academia and the government research laboratories work in close collaboration for the discovery of new herbal drugs. Millions of Indians use herbal drugs regularly, as spices, home-remedies, health foods as well as over-the-counter (OTC) as self-medication or also as drugs prescribed in the non-allopathic systems[8]. More than 500,000 non-allopathic practitioners are trained in the medical colleges (>400) of their respective systems of health and are registered with the official councils which monitor professionalism.

Research approach to herbal Products

The path of reverse pharmacology, arising from Observational therapeutics is complementary to other approaches for natural drug development (Fig. 1).

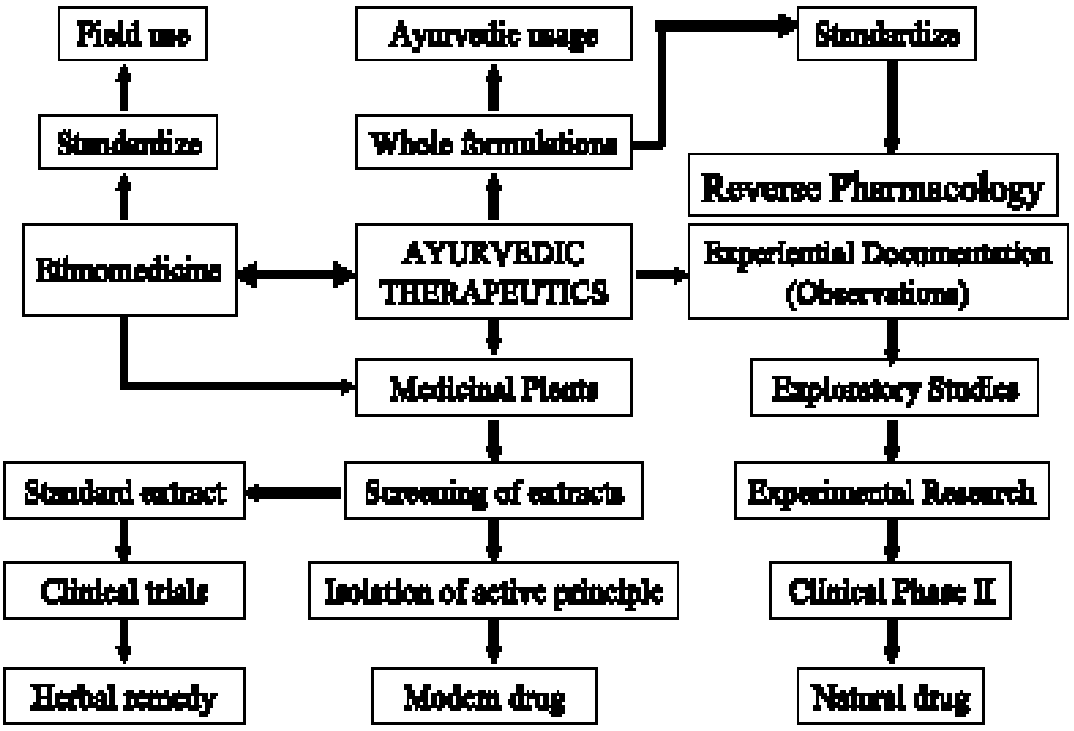

Fig.1. Research Approach to herbal products (R&D Path for Natural Products).

The diversity of medical uses of plant is at times daunting for a new entrant to the field. But for a multidisciplinary research and a development network the options of research approach provide deep motivation for identification of new pharmacophores. Besides expanding the herbal therapeutic and preventive armamentarium, new pharmacophores may help to evolve new targets of drug action as well as a possibility for combinatorial chemistry on the novel pharmacophores. For example, curcumin has been a target molecule for a significant endeavour for a large number of combinatorial compounds. The Council of Scientific and Industrial Research (CSIR), in India has initiated sizeable and meaningful efforts for the development of herbal-based formulations for diabetes, arthritis and hepatitis by a national network programme[9]. Interesting and novel activities have been detected with the selected plants and some of the active ingredients of therapeutically demonstrable effects e.g. glycaemic control and inhibition of HbA1c (glycosylated haemoglobin) level coupled with a reduction in *in vitro* formation of Amadori products. The diverse approaches to herbal drugs have led to interesting hits and novel activities, which need further in depth drug development efforts, both as herbal as well as new single molecule drugs.

Activity of interesting Ayurvedic Research findings/drug developments

There is a vast literature and research finding on Ayurveda in Sanskrit, Hindi and regional languages that is often not accessible to the other language groups. The mongraphs and books in English are also available. The diverse approach to herbal drugs have led to interesting hits and novel activities, which need further in depth drug development efforts, both as herbal as well as new single molecule drugs. Table 2 lists the activity of ten of interesting Ayurvedic drugs.

Table 2. Activity of Interesting Ayurvedic drugs.

S. No	Botanical name	Activity	Medline hits	Google hits	Key reference
1	*Phyllanthus emblica*	Antiaging	69	71000	[10]
2	*Withania somnifera*	Phytoestrogen	176	162000	[11]
3	*Mucuna pruriens*	Parkinsonism	53	155000	[12]
4	*Aegle marmelos*	Irritable Bowel	51	63300	[13]
5	*Centella asiatica*	Cognition	136	478000	[14]
6	*Berberis aristata*	Antimicrobial	15	58500	[15]
7	*Ricinus communis*	Anti inflammatory	2146	665000	[16]
8	*Azadirachta indica*	Anti malarial	333	342000	[17]
9	*Zingiber officinalis*	Anti nausea	368	266000	[18]
10	*Glycyrrhiza glabra*	Anti ulcer	161	396000	[19]

Some important Herbal Research Institute / Centres in India

A large number of academic, industrial and government institutes are conducting research on the medicinal plants of India. There has been no systemic review of the massive work that is available from this nation. Many international data-bases and web-sites do not cover even the work published in the Indian Journals. Hence, there is a global lack of awareness of the mass and nature of work carried out on diverse aspects viz. ethnobotany, phytochemistry, pharmacognosy, pharmacology, clinical trials, safety studies and formulation-research. A short list of some of the eminent institutes which are active in herbal research and Ayurveda are given in Table 3.

Table 3. Important herbal research institute/ centres in India

S. No	Name of the institute / centre	Location
1	CCRAS (Central Council for Research in Ayurveda and Siddha)	New Delhi
2	RRL (Regional Research Laboratory) (CSIR)	Jammu-Tawi
3	NBRI (National Botanical research Institute) (CSIR)	Lucknow
4	Gujarat Ayurveda University	Jamnagar
5	Bhavan's SPARC	Mumbai
6	National Institute of Ayurveda	Jaipur
7	ACARTS	Mumbai
8	Arya Vaidya Shala	Kottakal
9	Interdisciplinary School of Health Sciences	Pune
10	Banaras Hindu University	Varanasi
11	CIMAP (Central Institute of Medicinal and Aromatic Plants)	Lucknow
12	ICMR (Indian Council for Medical Research)	New Delhi
13	National Medicinal Plants Board	New Delhi
14	Indian Drug Manufacturers	Mumbai

15	Regional Medical Research Centre (ICMR)	Belgaum
16	PERD Centre (Pharmaceutical Education and Research Development)	Ahmedabad
17	CCRUM (Central Council for Research in Unani Medicine)	New Delhi
18	NISCOM (National Institute of Science Communication)	New Delhi
19	IMPCOPS (Indian Medicinal Practitioners Co-operative Pharmacy and Stores Ltd.,)	Chennai
20	IHMMR (Indian Institute of history of Medicine and Medical Research)	New Delhi
21	Zandu Foundation	Mumbai
22	Pharmexcil	Hydrabad
23	Chemexcil	Mumbai
24	CRDI (Central Drug Research Institute) (CSIP)	Lucknow
25	IMPLANT Centre (Inter-University Medicinal Plant Laboratory for Analysis, Nature and Therapeutics)	Rajkot
26	NIMHANS (National Institute for Mental health and Neurosciences)	Bangalore
27	Panjab University	Chandigarh
28	LM College of Pharmacy	Ahmedabad
29	NBPGR (National Bureau of Plant Genetic Resource)	New Delhi
30	NPRC (Nicolas Piramal Research Centre)	Mumbai
31	NCL (National Chemical Laboratory)	Pune
32	TBGRI (Tropical Botanical Garden & Research Institute)	Thiruvanandapurum
33	Podar Hospital	Mumbai
34	BSI (Botanical Survey of India)	Kolkata
35	FRHLT (Foundation for Revitalisation of Local Health Traditions)	Bangalore
36	IASTAM (International Association for the Study of Traditional Asian Medicine)	Mumbai
37	ADMA (Ayurvedic Drug Manufacturing Association)	Mumbai

Bio informatics on medicinal plants and traditional knowledge

New approaches could be used to study the resources of medicinal plants and the achievments reported for recent several years in bioinformatics and genomics. Bioinformatics might give some ideas that the diversity of medicinal plants in gene bank, in which we can selected some useful genes, determined a combination of the number of medicinal plants and their relative abundance. More and more problems might be discovered and solved in the research of medicinal plants with the tools of bioinformatics.

Different Databases used for Medicinal plants in India

a. Medicinal Plants Master Database

A comprehensive master database on medicinal plants of India has been systematically built up at Foundation for Revitalisation of Local Health Traditions (FRLHT) over the last 8 years. Currently, this database incorporates more than 7,500 botanical names which are linked to more than 1,40,500 vernacular names in 13 different languages like Tamil, Kannada, Malayalam, Hindi, Sanskrit, etc. Each such correlation can be traced back to a published reference. This database also incorporates more than 10,000 authentic digital images of plants duly linked to their botanical names. An important feature of this database is a fully-referenced distribution database which provides information on geographical distribution of nearly 6,000 plant species. Through a system of assigning a unique ID number to each botanical name and linking various aspects of information, for each species, to this unique ID, data relating to several different aspects like propagation, trade, pharmacognosy etc can be quickly accessed for a specific plant entity with search being initiated with the help of a botanical or vernacular name. This multi-faceted database forms the backbone for undertaking and promoting sustainable use and informed conservation action for native medicinal plant species and also acts as a platform for designing various research projects relating to the management of this valuable natural resource. This database is also linked to referenced information on the plant materia-medica of traditional systems of medicine as well as to pharmacognosy and pharmacology of the plant entities.

b. Pharmacognosy database on Indian medicinal plants

A computerized database called Labguru has been created for storing and retrieving referenced literature on pharmacognosy and pharmacology of medicinal plants. Labguru is a stand-alone database with an easy-to-use interface, linked to the master database. This database is a valuable literature source for researchers and industry alike. Data compilation is from published sources such as texts and on-line databases. This is an ongoing evolving activity in the laboratory at FRLHT.

c. Database on metals and minerals used in Indian medicines

Mineral and metal medicine is used by traditional practitioners all over India. These are potent medicinal materials which need accurate identification of materials and careful processing for their proper use. Therefore it was decided to develop a user-friendly and easily retrievable database on mineral and metal medicine by compilation of relevant references from authentic traditional texts of Ayurveda that are difficult to procure at one place for most users. Correlating the traditional names of metals minerals to modern geological entities helps to understand the identity of the minerals used.

d. AYUSH Databases

FRLHT in the last 10 years has been documenting and developing traditional knowledge databases on the materia medica of Indian systems of medicine. Medicinal plant databases have been already initiated on Ayurveda, Siddha, Unani system and Homoeopathy. The current FRLHT databases have screened a limited number of the known medical texts written across the period 1500 BC to 1900 AD and therefore much work yet remains to be done. In the next 5 years AYUSH will initiate a new database work on diagnostics and other speciality areas like *panchakarma* and *rasayana*, as these fields are critical for effective application of Ayurveda and Siddha. The main goal of the databases is to serve the needs of students and teachers of Indian systems of medicine, medical practitioners, researchers, community enterprises, community health NGOs and pharmaceutical companies.

e. Database of plants of Susruta Samhita

The database of plants of Susruta Samhita has 9,650 references. This data has been converted from the previous data environment to the present one to support access to various database tools. A checklist of the plant names was prepared and a report is made available in Sanskrit and English scripts.

f. Database on plants of Siddha medicine

The bilingual database has an extensive collection of information pertaining to therapeutic information of plants mentioned in 5 texts of 2,350 records, simple remedies mentioned in 6 texts of 1,800 records, formulation data of 3,013 records and 36,000 records of dictionary file which has Tamil names of plants. A separate nighantu file in Tamil script and a glossary of the technical terms are also incorporated in this database.

g. Database on plants of Homoeo medicine

This database could complete compilation of plants and products information of 80 plants mentioned in Homoeo medicine from 15-20 sources as text document.

h. Database on plants of Unani medicine

A hard copy of the Arabic and Urdu names appearing in the classical texts of Unani medicine was prepared from the FRLHT's nomenclature database. Verification on botanical names and spellings of Arabic names and Unani names were carried out.

i. Databases for assessment of local health traditions

The web-based Referral Browser basically aims to provide support for assessment of folk health traditions. This will help to promote best health-related practices in a specific area for human, plant and animal health care. The browser will procure references from Ayurveda, Siddha, Unani and modern pharmacology for a resource used in folk health practice and is subjected to evaluation/assessment. The web-based Referral Browser basically aims to provide support for assessment of folk health traditions. This will help to promote best health-related practices in a specific area for human, plant and animal health care. The browser will procure references from Ayurveda, Siddha, Unani and modern pharmacology for a resource used in folk health practice and is subjected to evaluation / assessment.

Genomics of Phytomedicine Research

Microarray

DNA microarray is an orderly arrangement of thousands of oligonucleotides or identified sequenced genes printed on an impermeable solid support, usually glass, silicon chips or nylon membrane. A number of terms such as DNA arrays, gene chips and biochips are often used to describe these devices. The DNA microarray field is a combination of several technologies, including automated DNA sequencing, DNA amplification by PCR, oligonucleotide synthesis, nucleic acid labeling chemistries and bioinformatics. Two most common types of DNA microarrays include one in which the DNA (in the form of a single stranded short oligonucleotide) is synthesized in situ using photolithographic or other techniques and another where the DNA (usually in the form of a cDNA or full-length ORF) is post-synthetically attached to a solid support [20, 21]. Depending on the kind of probe (immobilized DNA) used to generate the array and, ultimately, the information that is derived from it; DNA microarrays are used for different applications [22, 23] . As a definition in the context of microarrays, a 'probe' is the (partial) genomic sequence of a gene deposited and fixed on the Microarray, whereas the

'target' is the biological sample material. Although there are many protocols and types of microarray experiments, the basic steps involved in any microarray experiment are isolating RNA or mRNA from appropriate biological samples; applying a fluorescent tag to the RNA or cDNA copy of it; hybridizing the labeled RNA or cDNA (target) to a microarray (probe) for a period of time after which the excess is washed off; scanning the microarray under laser light and data analysis using appropriate software. A brief description of three basic types of DNA microarray experiments and their applications is provided in Table 4.

Table. 4. Basic types of DNA microarray experiments

Microarray type	**Brief description**	**Applications**	**References**
Comparative genomic hybridization (CGH)	Detect chromosomal aberrations	Tumor classification Disease diagnosis Risk assessment	[24-30]
Expression analysis	Analysis of gene expression levels	Drug development Drug response Tracking disease progression Therapy development Drug mechanism of action	[31-37]
Mutation/polymorphism Analysis	Detect mutations/polymorphisms in gene sequence	Drug development Tracking disease progression Disease risk assessment Genotyping Species identification Population genetics	[38-43]

Applications of DNA microarrays in Herbal Drug Research and Development

DNA microarrays may provide a suitable high-throughput platform for research and development of drugs from natural products. In natural products a broad repertoire of chemical entities acts together on multiple targets that make it necessary to study the changes in expression of multiple genes simultaneously. Novel technologies such as SAGE and DNA microarrays allow rapid and detailed analysis of thousands of transcripts, providing a revolutionary approach to the investigation of gene expression. In this chapter, we discuss the applications of DNA microarray technology in herbal drug research and development with suitable examples. There are three main applications of DNA microarrays: first, in pharmacodynamics for discovery of new diagnostic and prognostic indicators and biomarkers of therapeutic response; elucidation of molecular mechanism of action of a herb, its formulations or its phytochemical components and identification and validation of new molecular targets for herbal drug development. Second, in pharmacogenomics for prediction of potential side-effects of the herbal drug during preclinical activity and safety studies; identification of genes involved in conferring drug sensitivity or resistance and prediction of patients most likely to benefit from the drug

and use in general pharmacogenomic studies. Third in pharmacognosy for correct botanical identification and authentication of crude plant materials as part of standardization and quality control. These applications are described here with some examples[44-47]. Figure 2 shows applications of DNA microarrays at various stages of a typical drug discovery pipeline.

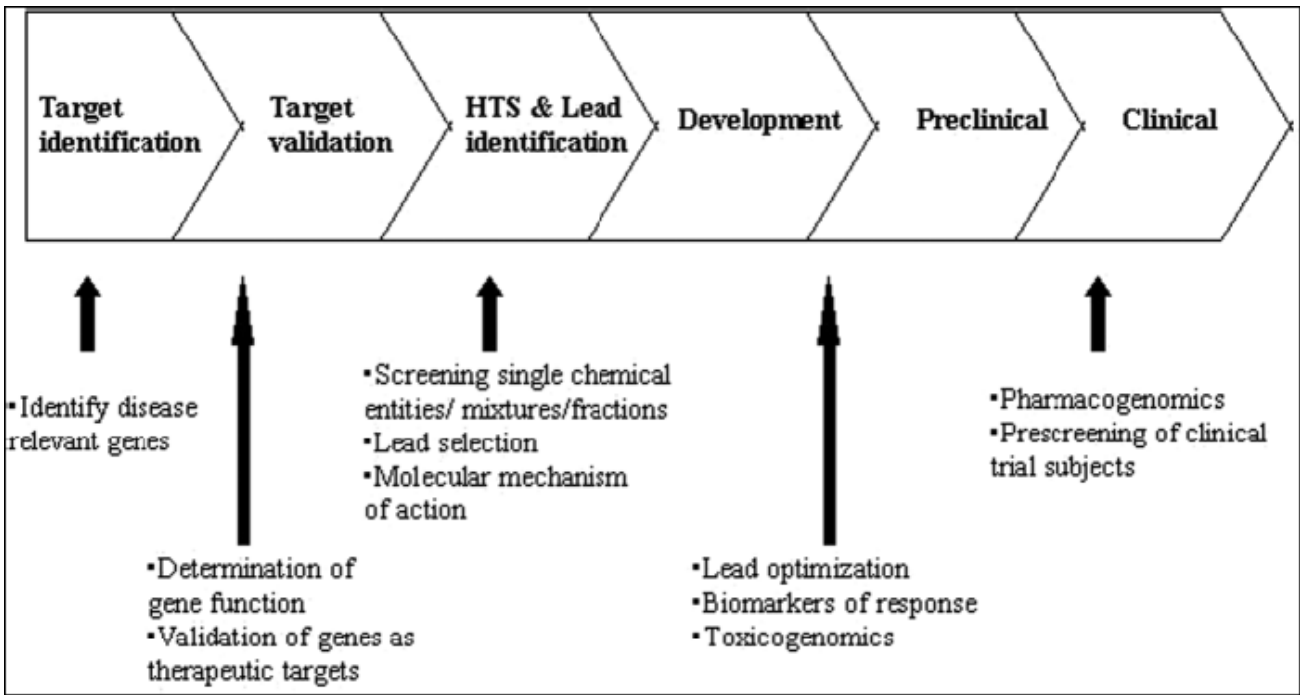

Fig. 2. DNA Microarray: applications in natural product drug discovery and development.

Metabolomics of Phytomedicine Research

Metabolomics, including both targeted and global metabolite profiling strategies, is fast becoming the approach of choice across a broad range of sciences including systems biology, drug discovery, molecular and cell biology, and other medical and agricultural sciences [48-50]. New analytical and bioinformatics technologies and techniques are continually being created or optimized, significantly increasing the crossdisciplinary capabilities of this new biology. The metabolomes of medicinal plants are particularly a valuable natural resource for the evidence-based development of new phytotherapeutics and nutraceuticals. Comparative metabolomics platforms are evolving into novel technologies for monitoring disease development, drug metabolism, and chemical toxicology. An efficient multidisciplinary marriage of these emerging metabolomics techniques with agricultural biotechnology will greatly benefit both basic and applied medical research. In the plant research field, metabolite profiling was first used as a diagnostic technique to determine the mode of action of herbicides on barley seedlings[51]. The concept of the 'metabolome' was first reported in 1998 as a way to quantitatively and qualitatively measure specific or defined phenotypes to assess gene function in yeast[52] and to discuss the interplay between the global metabolite pool and specific environmental conditions in Escherichia coli[53]. In the decade since these early beginnings, the use of metabolomics technologies in biological research expanded exponentially. If one just looks quickly at PubMed literature search results, metabolomics-related research articles have increased from some 40 published articles in 2002 to 100, 170, 200 and >250 articles in the years 2004, 2005, 2006 and 2007, respectively. Owing to its great utility in a variety of basic and applied research fields, metabolomics has quickly become a universal

tool and a key component for systems biology studies in medical research. Systems biology research using genomics, proteomics, and metabolomics approaches is investigating characteristic molecular signatures for disease diagnosis, prognosis, and therapeutics[54]. Recent developments in technology platforms and experimental approaches for metabolomics studies in drug development are outlined in this review. We also urge the greater use of metabolomics in the development of active secondary metabolites from medicinal plants as novel or improved phytotherapeutic agents. Wang *et al.,*[55] pointed out that metabolomics could provide the needed links between the complex chemical mixtures used in TCM and molecular pharmacology. Phytocompound-specific signatures in gene and/or protein expression profiles can also be highly useful in pharmacological standardization, such as their use in 'biological fingerprinting' of medicinal plant extracts (i.e. bioactivity spectra of phytoextracts or phyto-compounds versus their medicinal efficacy in test animal or human systems)[56-57]. Metabolomics approaches using GC–MS, LC–MS, or 2D NMR are an effective tool for quality control of medicinal plants or herb medicinal products[58-60]. In addition, they may provide proof of the toxicology/safety measures of specific phytopreparations after metabolism in test animals/humans[61]. Some key aspects of the technology used in a metabolomics approach to herbal medicine research are outlined in Figure 3.

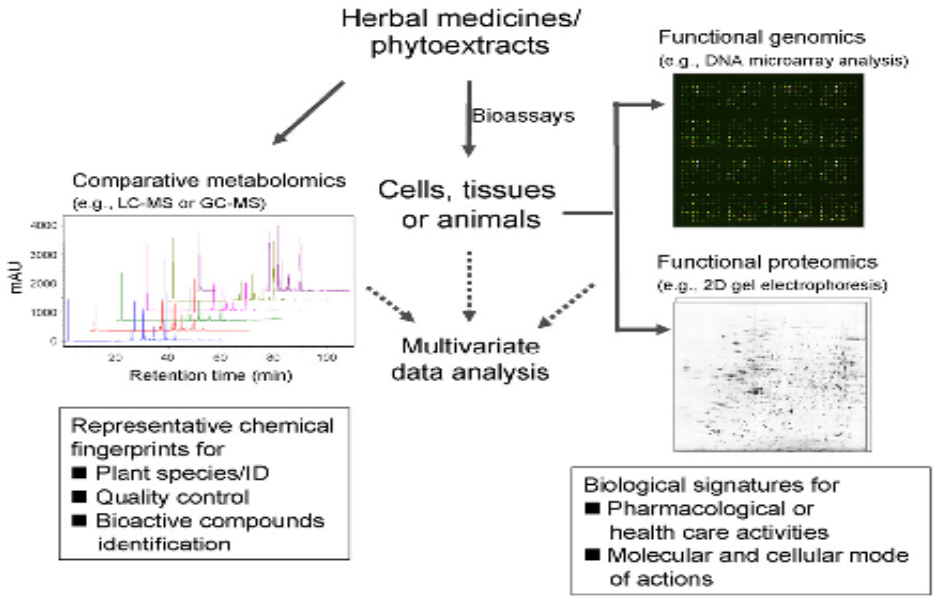

Fig.3. Key features of the technologies used in metabolomics for herbal medicine research.

Conclusion, future challenges and Perspectives

Herbal medicine, in addition to their traditional values, also hold great public and medical interest worldwide as sources of nutraceuticals or novel lead compounds for drug development. It's very important that the herbal scientist should bring the traditional knowledge to use the modern technology and to reach the modern knowledge such as allopathy medicine. A thorough integration of information from genomics, proteomics, and metabolomics is expeted to provide solid evidence-based scientific rationales for the development of modern phytomedicines. The search for active phytocompounds will

be greatly advanced by the combination of various metabolomics approaches with an array of bioactivity assays in mammalian systems to differentiate between plant species, tissues, or phytopreparations, and to identify novel lead compound candidates for future development. In a complementary development, the use of metabolome-refined herbal extracts with other biochemical components in combination, rather than as isolated single compound(s), may prove to be very useful as broader and holistic therapeutical or pharmacological agents for a variety of human health care applications.

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