

Strategies for Revitalization of Traditional Medicine

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Abstract: Traditional medicine (TM) plays an inevitable role in drug discovery and development. Most of the therapeutically useful molecules used in the present day are inspired from TM. Herbal drugs are the oldest forms of medicines used for the treatment of various ailments and the TM of every country has a long history of their usage. To develop more data on their quality, safety, and efficacy, so also to improve the consumer's need of modern days several thrust areas of research are to be focused on the development of TM. Based on the above concept, a paradigm shift is required for the revitalization of TM. These facts along with the modern scientific approaches, molecular tools, and strategies make it necessary for TM to be revitalized. Confluenting several strategies with the technological and scientific developments including pharmacogenomics, nutrigenomics, system biology, and related approaches, the scientific potential of TM can be explored further with international coordination and collaborations.

Key words: alternative medicine; Ayurveda; Chinese medicine; drug discovery; herbal resurgence; Indian medicine; Omic technology; system biology; traditional medicines

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Introduction

Traditional medicine (TM) implies generally to those medical and healthcare systems practiced in a traditional manner and are not presently considered to be part of conventional Western medicine. This discipline has evolved over years by drawing on the religious beliefs and social structures of numerous indigenous peoples, by exploiting natural products in their environments, and more recently by developing and validating therapeutic and preventive approaches using the scientific method (Mukherjee *et al.*, 2009; Debas, Laxminarayan, and Straus, 2005). Although TM are not always evidenced with scientific documents as like as the conventional medicine, it is quite popular among people due to their practical benefits, traditional beliefs, economical advantage and easy access and other reasons which have a regional, religious, and social basis.

Even though TM has to virtually cross miles in proving its therapeutic efficacy scientifically, it is only

due to its hugeness and wide applicability to a variety of disease and targets according to the synergy concept as discussed in this chapter. In the normal evolution of the concept, the growth of conventional medicine has made the herbal drugs a setback due to the absence of proper scientific evidence (Mukherjee and Wahile, 2006). Nowadays, with the development of modern analytical tools and the improved concepts on disease and its cure, the researchers on TM have more burdens to revitalize the system to its golden period. In spite of all these setbacks, TM remains with a constant growth in the global market. With the developing attention of the Western world towards the herbal drugs in general and TM in particular, it is necessary to take appropriate measures to bring back the concept of TM as a medicine to treat. In a view to revitalize TM several main research areas should be focused and adequate novel concepts and/or approaches should be developed in line with the conventional approaches so that the appropriateness of the system can

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be proved scientifically without any doubt.

TM is composed of several systems of medicine from different parts of the world. This includes traditional Chinese medicine (TCM) from China, Ayurveda, Siddha, and Unani systems from Indian systems of medicine (ISM), and several other systems derived from different parts of the world. In this article we will highlight mostly on the TCM and ISM. It has been estimated that two-thirds of the world's population seek healthcare from sources other than conventional biomedicine. While many of these individuals undoubtedly seek their remedies from various TM including Ayurveda, TCM, Kampo, native American medicine, traditional Hawaiian medicine, Unani, Latin American folk systems, etc (Pal, 2002).

TCM is derived mostly from the philosophy that informs Taoist and Buddhist thought, and reflects the traditional Chinese belief that the life and activity of individual human beings have a close relationship with the environment on all levels (Benn, 2002). This includes experience of treatment and theories of medicine, such as the meridian theory, as well as many other issues, including physiology, pathology, prevention, diagnosis, treatment, acupuncture and moxibustion, and tuina, etc.

To compensate the global market demand of herbal drugs, scientific and clinic experiments in TCM are continuously advancing. The achievements have been made in areas such as in circulating paths of meridians; in Zheng-syndrome, in diagnostic indexes; in therapeutic principles, in healing emergency patients with shock, acute disseminated intravascular coagulation, acute myocardial infarction, and acute renal failure. TCM has been known as efficient treatment of diseases like tumors, cardio-cerebro-vascular, bone fracture, etc. As an example, the theory of combination of mobilization and immobilization was enforced for treatment of bone fracture; Non-antibacterial compound prescriptions are still being used in treatment of bacterial infection. *Fuzheng Guben* compound prescriptions cause the shrink age of the mass of cancer in the treatment of cancers. TCM provides an advantage that non-surgical approach to the treatment of acute abdomen, which can be easily adopted in TM. These several modern techniques have been adopted into the system, which ultimately gave a positive result (Feng *et*

al, 2006). Demand for Chinese herbal products is surging not just domestically as consumer power increases, but also overseas as China's economy is liberalized and TM is more widely accepted.

India has an ancient heritage of TM. Materia medica of India provides a wealth of information on the folklore practices and traditional aspects of therapeutically important natural products. Indian TM is based on various systems including Ayurveda, Siddha, and Unani (ASU). Each of these traditional systems has unique aspects, but there is a common thread among their fundamental principles and practices in the use of natural products mostly herbs. With the emerging interest in the world in adopting and studying the traditional system and in exploiting their potentials based on different healthcare systems, the evaluation of the rich heritage of the TM is essential (Mukherjee, 2005).

Ayurveda, accepted to be the oldest treatise on medical systems, came into existence in about 900 B.C. According to Indian Hindu mythology, there are four Vedas written by the Aryans—Rig Veda, Sama Veda, Yajur Veda, and Atharva Veda. Among these Rig Veda, the oldest, was written after 1500 B.C. The Ayurveda is said to be an Upaveda (part) of Atharva Veda, whereas the Charaka Samhita (1900 B.C.) is the first recorded treatise fully devoted to the concept of practice of Ayurveda. The Indian government and private sectors are trying their best to explore all the possibilities for the evaluation of these systems to bring out the therapeutic approaches available in the original system of medicine as well as to help in generating data to put these products on the national healthcare program (Mukherjee, 2003).

The Siddha system of India medicine is almost akin to Ayurveda. It is an ancient traditional system of medicine developed by 18 Siddhars who glorified human beings as the highest form of birth and believed that to preserve the human body was essential to achieve eternal bliss. Formulation in Siddha medicine includes the herbal products, inorganic substances, and animal products and leads to different formulations such as Chendooram (reddish powdered medicine), Choornam (powdered drugs), and Chunam (medications prepared by calcinations). The use of metals and minerals form an integral part of the Siddha system of therapy to cure diseases (Mukherjee, 2003). The Unani system of

medicine is known in different parts of the world by various names, such as Arat medicine, Greco-Arab medicine, Loniah medicine, Islamic medicine, and Oriental medicine. In this particular traditional system, single drugs or their combinations in raw form are preferred over a compound formulation. At present, the Unani system of medicine, with its own recognized practitioners, hospitals, and educational research institutions, forms an integral part of the national healthcare system in India (Mukherjee, 2002).

This article highlights on the present concept of TM, the thrust areas of research to be focused for drug discovery and development from TM in general from the alternative and complementary systems of medicine.

Drug discovery and development of leads from TM

In the past, there were numerous moieties from TM which had been screened for their efficacy and

found to be potent for the treatment of various pathologies. Biological activities of these molecules were covered a broad range of therapeutic areas. Few examples of drugs from TM would better explain the history of its own tradition. Several approaches on drug discovery and development from TM had been practiced by scientists from years together. Various databases had been developed for evaluation of this system of medicine (Fig. 1). Nature had given various benefits to the human kind which included treatment of the illness. The component isolated from willow bark (acetyl salicylic acid) in the year 1853, still enjoys its presence in therapeutics. Similarly, several therapeutically potential constituents were isolated from the plants such as artemisinin (**1**) (treatment of Malaria), vincristine (**2**), and vinblastine (**3**), camptothecin podophyllotoxin, etoposide, teniposide, and paclitaxel (used in treatment of cancer) (Cragg *et al*, 1993) (Fig. 2).

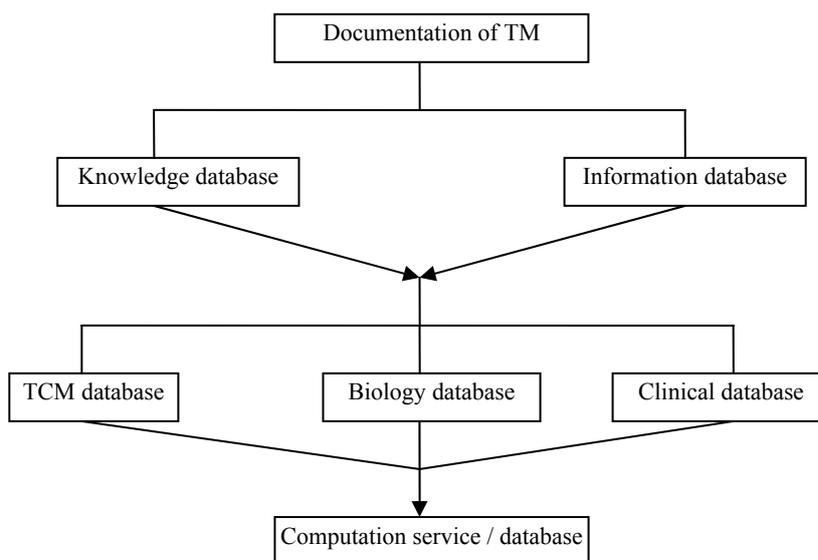


Fig. 1 Drug discovery approach through TM database

The Chinese plants *Ephedra sinica* Riedl and *E. equisetina* Bunge are used for the treatment of asthma and other bronchial conditions which led to isolation of ephedrine in 1923. It was the first in a very long line of bronchodilators/CV agents (Chen and Schmidt, 1930). Camptothecin was isolated from the Chinese ornamental tree *Camptotheca cuminata* Descne (Potmeisel and Pinedo, 1995). The sodium salt of camptothecin was advanced to clinical trials by NCI which led to the approved agent irinotecan. An antimalarial source, *Artemisia annua* L. has been used for decades in China since 1972, the active agent, artemisinin (**1**) (a

sesquiterpene endoperoxide) has been isolated and identified (Clark, 1996). Using the basic structure of artemisinin (**1**), many semi-synthetic compounds were made with the aim of optimizing the pharmacology of the base molecule, leading to the identification of artemether (dihydroartemisinin), a potent antimalarial agent that is now widely used across the globe.

Several therapeutically potent constituents derived from Chinese materia medica have been categorized in Table 1. Sphenadilactones (**4**) exhibited anti-HIV activity in the inhibition assay for the cytopathic effects of HIV-1IIB (Ollivier *et al*, 2005). The roots of *Flueggea virosa*

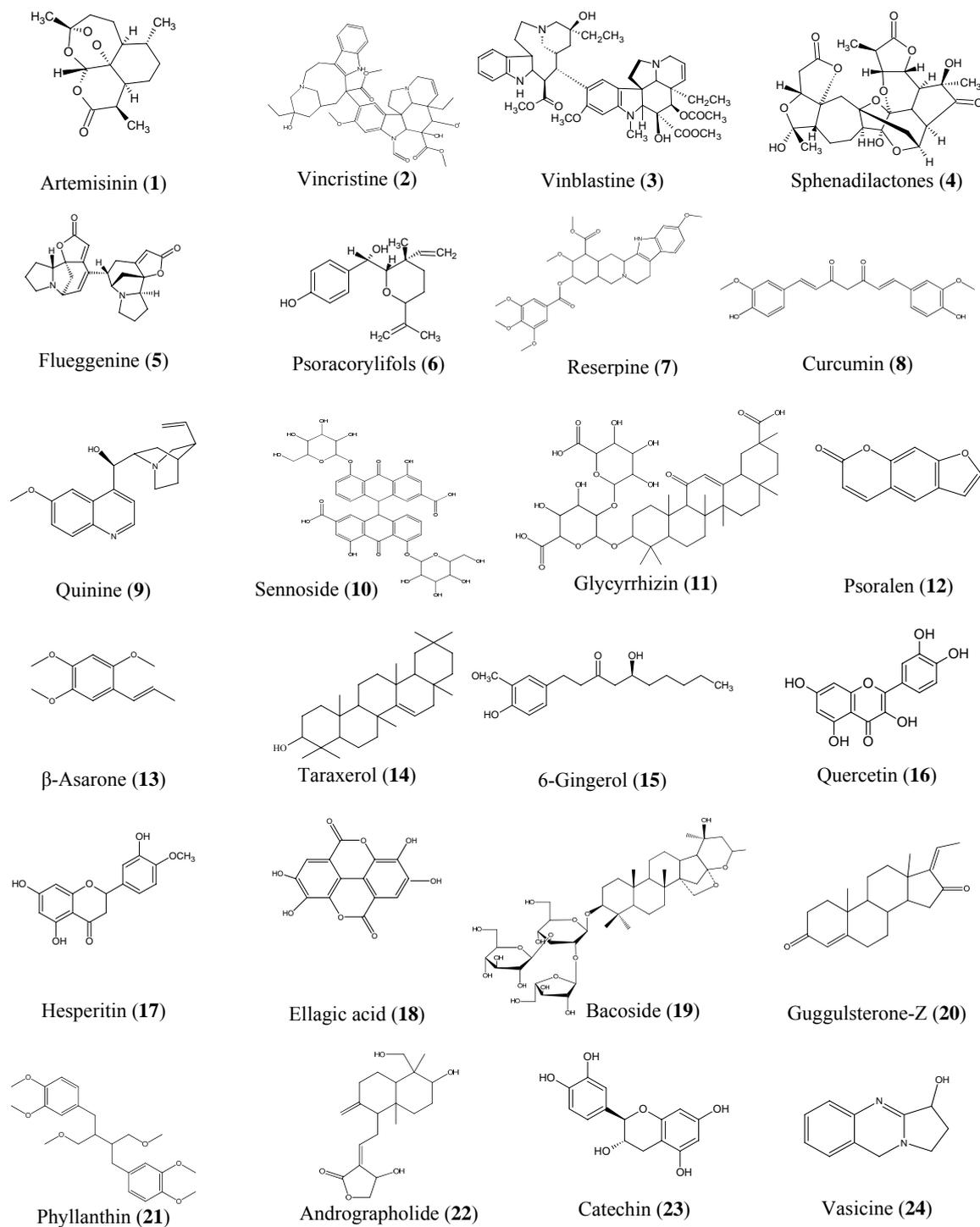


Fig. 2 Structures for some phytoconstituents

(Roxb. ex Willd.) Voigt. yielded Flueggein A and B. Only Flueggein A (5) exhibited weak activity against the murine leukemia P-388 cells, but flueggein B was observed to be inactive (Liu *et al*, 2005). Psoracorylifols A–E (6) (pyran derivatives) were isolated from the seeds of *Psoralea corylifolia* L., a well-known traditional Chinese medicine showed important inhibitory activity

against the strains of *Helicobacter pylori* (Weissman and Leadlay, 2005).

It is obvious that the Chinese herbal formulations are being used and their standards are being upgraded for the treatment of several diseases. Table 2 renders a few examples of the Chinese herbal formulations used in TM for different ailments. There is considerable interest

Table 1 Significant new chemical entities reported in the literature (2005–2006)

Compounds	Chemical nature	Source	Pharmacological effect
sphenadilactones A	nortriterpenoid	<i>Schisandra sphenanthera</i>	anti-HIV-1 activity in the inhibition assay for the cytopathic effects of HIV-1III B
sphenadilactones B	nortriterpenoid	<i>Schisandra sphenanthera</i>	anti-HIV-1 activity in the inhibition assay for the cytopathic effects of HIV-1III B
flueggenines A	indolizidine alkaloid	<i>Flueggea virosa</i>	exhibited weak activity against the murine leukemia P-388 cells
flueggenines B	indolizidine alkaloid	<i>Flueggea virosa</i>	observed to be inactive
psoracorylifol A	pyran derivative	<i>Psoralea corylifolia</i>	important inhibitory activity against two strains of <i>H. pylori</i> (SS1 and ATCC 43504)
psoracorylifol B	pyran derivative	<i>Psoralea corylifolia</i>	important inhibitory activity against two strains of <i>H. pylori</i> (SS1 and ATCC 43504)
psoracorylifol C	pyran derivative	<i>Psoralea corylifolia</i>	important inhibitory activity against two strains of <i>H. pylori</i> (SS1 and ATCC 43504)
psoracorylifol D	pyran derivative	<i>Psoralea corylifolia</i>	important inhibitory activity against two strains of <i>H. pylori</i> (SS1 and ATCC 43504)
psoracorylifol E	pyran derivative	<i>Psoralea corylifolia</i>	important inhibitory activity against two strains of <i>H. pylori</i> (SS1 and ATCC 43504)

Table 2 Chinese formulations used in TM for different ailments

Formulations	Constituents	Application	Reference
Penta Herbs formula (PHF)	<i>Cortex Moutan</i> , <i>Paeonia suffruticosa</i> , <i>Cortex Phellodendri</i> , <i>Phellodendron chinensis</i> , <i>Flos Lonicerae</i> , <i>Lonicera japonica</i> , <i>Herba Menthae</i> , <i>Mentha haplocalyx</i> , <i>Rhizoma Atractylodis</i> , <i>Atractylodes lancea</i>	Management of eczema.	Chan <i>et al</i> , 2008
Baishouwu	<i>auriculatum</i> , <i>Cynanchum bungei</i> , <i>Cynoctonum wilfordii</i>	Induced gastric lesions and histamine-induced gastric acid secretion in rats. Study demonstrates the gastroprotective property of Baishouwu for the first time.	Shan <i>et al</i> , 2006
Shi-Bi-Lin (SBL) is modified from the classic formula <i>Cang-Er-Zi-San</i>	<i>Xanthium sibiricum</i> , <i>Angelica dahurica</i> , <i>Saposhnikovia divaricata</i> , <i>Mangolia biondii</i> , <i>Gentiana scabra</i> , <i>Verbena officinalis</i>	SBL relieved symptoms of nose blockage among patients with perennial allergic rhinitis, and some aspects of the quality of life were also improved. chronic rhinitis, paranasal sinusitis and allergic rhinitis	Zhao <i>et al</i> , 2009
Kanbaku-taiso-to (KT)	<i>Glycyrrhizae Radix</i> , <i>Tritici Semen</i> , <i>Zizyphi Fructus</i>	KT has a sedative effect on the nervous system (i) KT lengthened the hexobarbital sleeping time; (ii) KT showed a marked prolongation of time to death in pentylenetetrazole (PTZ)-induced convulsions; (iii) locomotor activity was inhibited by 7-day continuous administration of KT.	Tsuda <i>et al</i> , 1986
Anti-aging formulation	<i>Herba Epimedii</i> , <i>Fructus Lycii</i> , <i>Radix Polygoni multiflori</i> , <i>Radix Cynanchi auriculati</i> , <i>Ganoderma</i> along with a composite prescription 'American Ginseng Royal Jelly'	Antiageing drug	Chen and Li, 1993
Xuan-Ju agent	<i>Formica Fusca</i> , <i>Herba Epimedii</i> , <i>Fructus Cnidii</i> , and <i>Fructus Lycii</i>	Xuan-Ju agent showed a marked inhibitory effect on edema in two models of inflammation in rats	Jia <i>et al</i> , 2003

among basic and clinical researchers in novel drugs with activity against several ailments. The vast history of TCM experience with medicinal herbs. These constituents plants may facilitate the identification of novel leading compounds from natural resources.

The use of ayurvedic drugs and formulations had always been an integral part of the treatment of different ailments in India. The research led on ayurvedic drugs yielded numerous drug candidates that are prevailing in the market. There are several plants (Table 3) of

Table 3 The Ayurvedic plant drug used in TM for different ailments

Ayurvedic drugs	Composition	Parts used	Active constituent	Applications	Reference
Brahmi	<i>Bacopa monnieri</i> Linn.	Dried whole plant	Bacoside (19)	Memory enhancer, antiasthmatic	Roodenrys <i>et al</i> , 2002
Guggul	<i>Commiphora mukul</i> (Hook ex Stocks) Engl.	Oleo-gum-resin	Guggulsterone-Z (20)	Hypolipidemic	Mukherjee and Mukherjee, 2005
Haridra	<i>Curcuma long</i> Linn.	Rhizome	Curcumin (8)	Antiinflammatory	Mukherjee and Mukherjee, 2005
Bhumyamalaki	<i>Phyllanthus amarus</i> Schum and Thonn.	Whole plant	Phyllanthin (21)	Hepatoprotective	
Kaalmegha	<i>Andrographis paniculata</i> Wall. Ex Nees.	Aerial part	Andrographolide (22)	Hepatoprotective	Mukherjee and Mukherjee, 2005
Sirisa	<i>Albizia lebeck</i> Benth	Stem bark	Catechin (23), Albizia saponins	Antiallergic, anti-tussive	The Ayurvedic Pharmacopoeia of India, 2001
Vasaka	<i>Adhatoda vasica</i> Nees.	Leaves	Vasicine (24)	Anti-asthmatic, bronchodilator	Mukherjee and Mukherjee, 2005
Tulasi	Ocimum Sanctum	Dried leaf	Carvacrol, nerol	To treat respiratory complications	The Ayurvedic Pharmacopoeia of India, 2001
Katuka	<i>Picrorhiza kurroa</i> Royale ex Benth	Dried rhizome with root	Kutkin	Antiasthmatic	The Ayurvedic Pharmacopoeia of India, 2001

ayurvedic origin with potential therapeutic activity, which are widely used as ayurvedic medicine. The government of India has taken very effective steps in developing the quality, safety, efficacy, and practice of herbal medicine along with several regulatory measures. In fact several modern drugs used in the treatment of ailments like reserpine (7) from *Rauwolfia serpentina* (L.) Benth. ex Kurz, withanolide from *Withania somnifera* (L.) Dunal, curcumin (8) from *Curcuma longa* L., quinine (9) from *Cinchona officinalis* L., sennoside (10) from *Cassia angustifolia* Vahl, glycyrrhizin (11) from *Glycyrrhiza glabra* L., and psoralen (12) from *Ruta graveolens* L. have been developed from Indian medicinal plants (Mukherjee, Venhatesh and Gantait, 2009).

Several leading compounds have been isolated from ISM in our laboratory such as betulinic acid from *Nelumbo nucifera* Gaertn. [immunomodulatory agent], β -asarone (13) from *Acorus calamus* L. [AChE inhibitor], mahanimbine from *Murraya koenigii* (L.) Sprengel [AChE inhibitor], and tilianin from *Semecarpus anacardium* L. [hepatoprotective] (Mukherjee *et al*, 2009).

The development of drugs from ayurvedic plants is ongoing, with the pharmaceutical companies engaged in large-scale pharmacologic screening of herbs. 'Sushruta-Samhita', a Sanskrit text on Ayurveda written in 600 B.C. noted that the plant *Commiphora mukul* Hook. was useful

in the treatment of obesity and related diseases. *W. somnifera* is used as an adaptogen traditionally in India. This is also known as 'Indian Ginseng' which stimulates the body's immune system and stops inflammation. Combining the strengths of the knowledge base of complementary alternative medicines such as Ayurveda with the dramatic power of combinatorial sciences and high throughput screening will help in the generation of structure-activity libraries. This can further be explored through clinical trial, various pharmacovigilance studies, herbal therapeutics, and pharmacokinetics. In recent years, a confluence of spectacular advances in chemistry, molecular biology, genomics, and chemical technology and the cognate fields of spectroscopy, chromatography, and crystall-graphy may influence several therapeutically potent leading compounds from TM.

Thrust areas of research and development for drug

In order to revitalize the TM in line with the modern medicine, various strategic areas in medicine plant research are to be considered of global importance. Nowadays, scientists have been convinced that the integration of TM and modern tools would not only benefit their own development, but also help to fight against many complex diseases through development of new entities. Such a dedicated research would be beneficial only with support from advanced approaches and novel strategies (Mukherjee and Houghton, 2007).

Numerous methods exist in order to evaluate the quality of either natural or synthetic substances. Several *in vitro*, *in vivo*, and high throughput screening methods are currently involved in the traditional drug discovery approaches used worldwide by the researchers (Mukherjee, 2002). But the fact indicates that there is an insufficiency and lacunas among them. Few *in vitro* or *in vivo* models lack their own specificity either by design or by inbuilt limitations. The potential disadvantage of whole-cell-based assay methods is in *in vitro* experiments; Cell cultures are more variable and less sensitive, and more resource intensive due to extensive assay development time (Baker *et al*, 2007).

Role of analytical techniques in drug development

Suitable analytical tools are very much required to establish the quality control of herbal drugs used in TM. Quality control of TM plays an important role in its safety and efficacy so that the product can be marketed in regulated countries. The introduction of analytical tools in modern analysis is advancing day by day, which provides information with more accuracy and precision. Although considerable accuracy was maintained in the conventional analytical tools, most of them are semi

automated or manually operated so that they led to several inconsistencies in the analytical results obtained. But the modern tools available facilitate the automation process in the instrument thus reducing the manual errors and increasing the accuracy.

Among these tools, separation techniques like HPTLC and HPLC play an important role. Herbs and herbal preparations are particularly difficult to standardize due to their well known complexity. For marketing a TM product investigation of a chemical and biochemical composition of a plant material is necessary. Further, fingerprint analysis by HPTLC or HPLC is perceived to be a powerful tool to link the botanical identity to the chemical constituents of the plant. In combination with various types of microscopy, the fingerprint provides the means for checking the identity of the plant. From the number of chemical constituents present in a herb, particular bioactive marker compounds can be chosen to standardize the plant material. This concept is known as marker analysis. Several advantages of marker analysis and related techniques have been explained in Fig. 3. It is an important concept for which the chromatographic techniques are used in order to standardize the active extract.

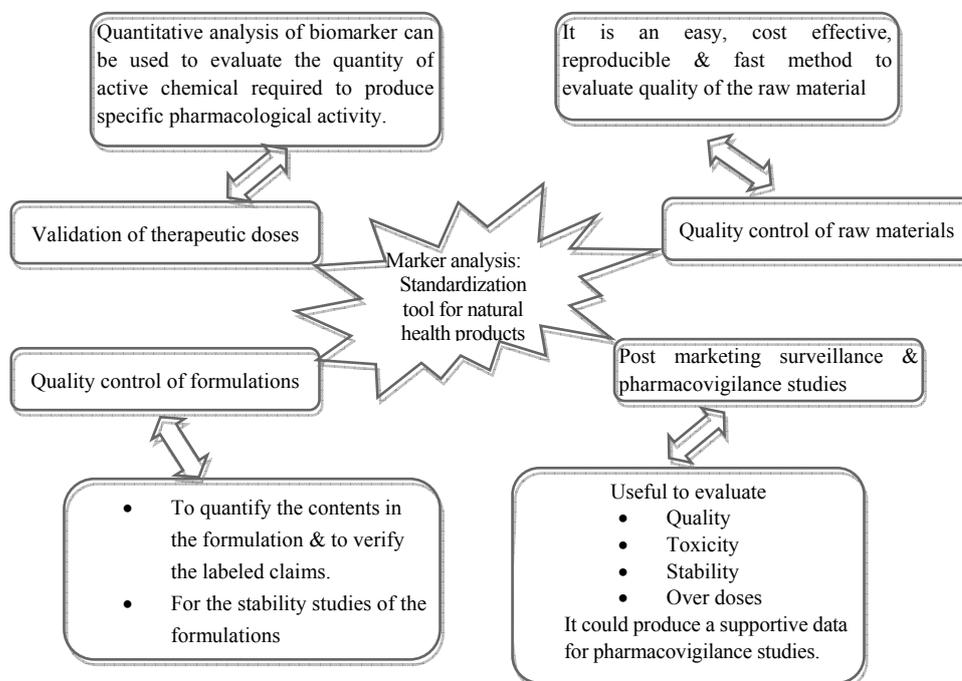


Fig. 3 Important applications of marker analysis

For the effective quality control measures, the identification of all the known bioactive compounds present in the marketed TM is essential. We have been working in

this field for development of marker profiles of herbs from Indian. Some simple and precise HPTLC method has been developed in our laboratory for the estimation and

validation of several phytoconstituents including taraxerol (**14**) in *Clitoria ternatea* L. (Kumar *et al*, 2008), gallic acid from *Terminalia chebula* Retz (Ponnusankar *et al*, 2009), trigonellin from *Trigonella foenum-graecum* L. (Satheeshkumar *et al*, 2009), and 6-gingerol (**15**) from *Zingiber officinale* Roscoe (Rai *et al*, 2006).

Similarly advance micro plate readers are used for several high throughput assays. It can facilitate minimal sample quantity and analyze large number of samples. To deal with an example, Mukherjee *et al* (2007a; 2007b) analyzed the hydroalcohol extracts from six herbs, *Andrographis paniculata* (Burm. f.) Nees, *Centella asiatica* (L.) Urb., *Evalvulus alsinoides* Linn., *Nardostachys jatamansi* (D. Don) DC., *Nelumbo nucifera* Gaertn., *Myristica fragrans* Hoult. used in ISM, for *in vitro* acetylcholinesterase (AChE) inhibitory activity based on Ellman's method in 96-well micro plates using AChE obtained from bovine erythrocytes. The results showed that the hydroalcohol extracts inhibited IC₅₀ value between 100 and 150 µg/mL. Apart from these basic analytical techniques, combined analytical approaches are utilized for the identification and quantification of metabolites. Several combined analytical techniques namely GC-MS, LC-MS, CE-MS, LC-MS-ESI, and FT-ICR-MS, etc. have been used.

Novel drug delivery system

The herbal formulation, which is one of the major segments of traditional system of medicine, contributes immensely to the positive health of an individual. There is need for development of some novel drug delivery system (NDDS) in herbal medicines for several reasons including targeted drug delivery, reduced dose, increased solubility, enhanced absorption, reduced elimination and metabolism of the drug.

Nano-particulate drug carriers, including a class of particles with a diameter of 10–1000 nm, are drug-loaded particles prepared by taking natural polymer or synthetic chemicals as the carrier. Compared to micrometer size carriers, nanocarriers provide more surface area and have the potential to increase solubility, enhance bio-availability, improve controlled release, and enable precision targeting of the entrapped compounds to a greater extent. As a consequence of improved stability and targeting, the amount of material required to exert a specific effect when encapsulated or incorporated to nanocarriers is much less than the amount required when

unencapsulated. This is particularly useful when dealing with expensive phytomolecules. A timely and targeted release improves the effectiveness of phytomolecules, broadens their application range, and ensures optimal dosage, thereby improving cost-effectiveness of the product. Thus, implication of nanotechnology to TM plant materials may not only improve their bioactivity but also reduce the amount of the nanopharmaceuticals required and, thereby, decrease environmental degradation related with the harvesting of the raw products (Liu *et al*, 2008).

Most of the herbal medicines may be considered to have therapeutic effect, but may not have them to the desired extent or at desired dose or target. Most of the herbal medicines being less bio-available due to several factors like solubility problems which cause reduced absorption, rapid metabolism and excretion. Value addition of such herbal medicines can be achieved by using techniques like phytosomes. Phytosomes are advanced forms of herbal products that are better absorbed, utilized, and as a result produce better effects than conventional herbal extracts. Phytosomes are produced *via* a patented process whereby the individual components of a herbal extract are bound to phosphatidyl choline. Using this technology several phytomolecules have been targeted with in NDDS at our laboratory. These phytomolecules have been reported to have improved efficacy and bioavailability. These include phytomolecules like curcumin (**8**) (Maiti *et al*, 2007), quercetin (**16**) (Mukherjee *et al*, 2005), hesperitin (**17**) (Maiti *et al*, 2009), ellagic acid (**18**) (Venkatesh *et al*, 2009), etc. that have been proved to be more effective. Several bioavailability and pharmaco-kinetic studies of these molecules have been carried on. Based on these studies, several value added formulations have been prepared at our laboratory and evaluated for their *in vitro* release, *in vivo* serum concentration, and therapeutic efficacy.

Safety studies

“All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy” - Paracelsus (1493–1541)

General public believe that modern drugs are dangerous foreign chemicals with side effects while herbs are natural and safe. In fact, some herbs can also be dangerous and even cause serious diseases leading to

death, if used inappropriately. The complexity of herbal medicine preparations and the interpretation of bibliographic data on safety and efficacy reflecting the experience gathered during long-term use are best addressed by involving specific expertise and experience. Further, without the knowledge of the prescriber, consumer tends to consume the herbal products, along with prescription medicine which may lead to herb-drug interaction, *via* cytochrome enzymes. The cytochrome P450 isoenzymes (CYPs) predominantly present in liver but are also found in intestine, lungs, kidneys, brain, etc. Several isoforms, such as CYP1A2, CYP2C9, CYP2D6, and CYP3A4 appear to be most relevant for the metabolism of clinically significant drugs. The medical literature is replete with reports suggesting that the concomitant use of these phytomolecules along with prescription medicines/OTC products, which may alter human drug metabolism and pharmacokinetics, and may cause serious clinical adverse reactions. Manufacturer's evaluation of these supplements for toxicology, pre-clinical and clinical data is not compulsory, and is not subject to standard pharmaceutical criteria for safety (Mukherjee *et al.*, 2008).

The use of herbal medicine is ancient. Plant constituents are still backbone part of our pharmacopoeia because more than 50% of drugs used in various pharmacopoeia are obtained or derived from herbs (Bagnais *et al.*, 2004). If plants contain pharmacologically active compounds, they also contain toxic substances. Herbal toxicity may be for so many reasons. This may be due to wrong identification of the plant or if it is not properly identified. This may be, when the plants are contaminated with other drugs, hormones, or heavy metals. Toxicity may be due to the interaction of the herbal material with conventional drugs. Besides there are large number of clinical drugs reported to have potential hepato, renal, cardio toxicity, etc. during epidemiological and other prospective studies. Other agents, such as excipients present in formulation and herbal medicines which are consumed and often not disclosed, should also be taken into consideration for its toxicity (Larrey and Pageaux, 2005).

There have been several regulatory requirements in different countries relating to its safety and for assessing potential interaction between the phytoconstituents and other conventional medicines (Mukherjee and Saha,

2003). The regulatory agencies require the documentation on the interactions of the herbal medicine involving CYP isoforms before licensing. Using *in vitro*, *in vivo*, and *in silico* techniques, several phytoconstituents have been identified as inhibitors or inducers of cytochrome resulting in herb-drug interaction. Similarly, drug interaction between phytoconstituent and conventional medicines has also been reported. Few examples of such interaction of active compounds including allicin, quercetin, silymarin compounds, etc., have also been reported. Conventional pharmacokinetic literature generally deals with drug-drug interactions, but recently such interactions between phytoconstituents and prescription drugs have drawn attention, because of increasing physician awareness of the widespread adverse effects of undisclosed herbal use by the patients. Establishing the safety of herbs using cytochrome modulating enzymes will attract TM manufacturers' attention to the potential marketing benefit.

Efficacy studies

TM has a long history of traditional use. However, the efficacies of most of these are unproven. The lack of evidence does not necessarily mean that TM lacks efficacy or is unsafe. Some evidences of efficacy, safety, and quality, if they exist, for herbal medicines, are considered to be anecdotal, or empirical at best. Rarely it is subjected to the rigorous prospective randomized controlled trial. At most, evidence should be extrapolated only to preparations of the same herb with a very similar profile of constituents (Busse, 2000).

One of the fundamental principles of clinical pharmacology is the rigorous assessment of the mechanism of drugs, the efficacy, kinetics, and safety using evidence from well-designed studies. The safety and efficacy of the herbal products are also determined by the pattern and concentration of the chemical components they contain. However, most clinical trials of herbal medicine have focused on either standardized extracts of single herb or standardized formulae reflecting increased sponsorship of such studies by manufacturers in the increasingly important OTC market. Evidence from clinical studies of single herb extracts or standardized formulae cannot be generalized to individualized herbal medicine, and claims by practitioners that the latter has an evidence base are unacceptable (Guo, Canter, and Ernst, 2007).

In addition, no references to pharmacological and clinical data obtained with “concentrated extracts of different composition” should be made for traditional preparations. This would generate the wrong impression that safety and efficacy are comparable. In this context, instead of misusing the absence of reliable evidence as the green signal for commercial exploitation, experimental studies in this field should continue and should be supplemented with the new concept of herbal pharmacovigilance. By using the models of conventional pharmacovigilance, herbal pharmacovigilance aims at the detection of serious adverse reactions, at the quantification of their incidence, and at the identification of contributive and modifying factors. A classic and inexpensive tool of pharmacovigilance is spontaneous reporting, on a voluntary basis, by health professionals, consumers who observe or experience a suspected or possible adverse reaction during daily practice (Kayne, 2006).

Herbal practitioners, researchers, and manufacturers should take initiatives to make pharmacovigilance work properly in the same way as doctors reporting reactions to synthetic pharmaceuticals. They should come to recognize that the reporting of suspected adverse reactions to their herbal medicines is an act of courage, which will eventually increase rather than decrease the respectability of their profession. Herbal pharmacovigilance is not a negative tool but a neutral one, especially when it identifies a new serious herbal health risk. Pharmacovigilance can also be reassuring, however,

by providing evidence that certain herbal health risks are absent or negligibly small. It can help to booster one of the main features of phytotherapeutics, namely their relative safety when compared to conventional pharmaceuticals (Mukherjee *et al.*, 2008).

System biology approach

System biology intends to understand biological complexity by indifferent measurements of as many parameters as possible, without having any hypothesis (Weckwerth, 2003). The focus of the rising area of systems biology is to inquire the dynamics of all genetic, regulatory and metabolic processes in a cell and to understand the complexity of cellular networks (Kitano, 2002).

Adoption of systems biology approach would do much help for exploring the scientific connotation of TCM syndrome and the modernization of Chinese herbal medicine (Fig. 4). Its technological platforms, such as genomics, proteomics and metabolomics, provide powerful tools for the study on the essence of TCM syndrome and the function of herbal compound recipe. Scientifically and technologically validated botanical products may be explored on a fast track using innovative approaches like reverse pharmacology and systems biology, which are based on knowledge of TM. TM comprises of evolutionary process as communities to discover practice transforming techniques (Patwardhan, 2008).

The methods for carrying out metabolic modeling by means for collecting, storing, and analyzing metabolomic

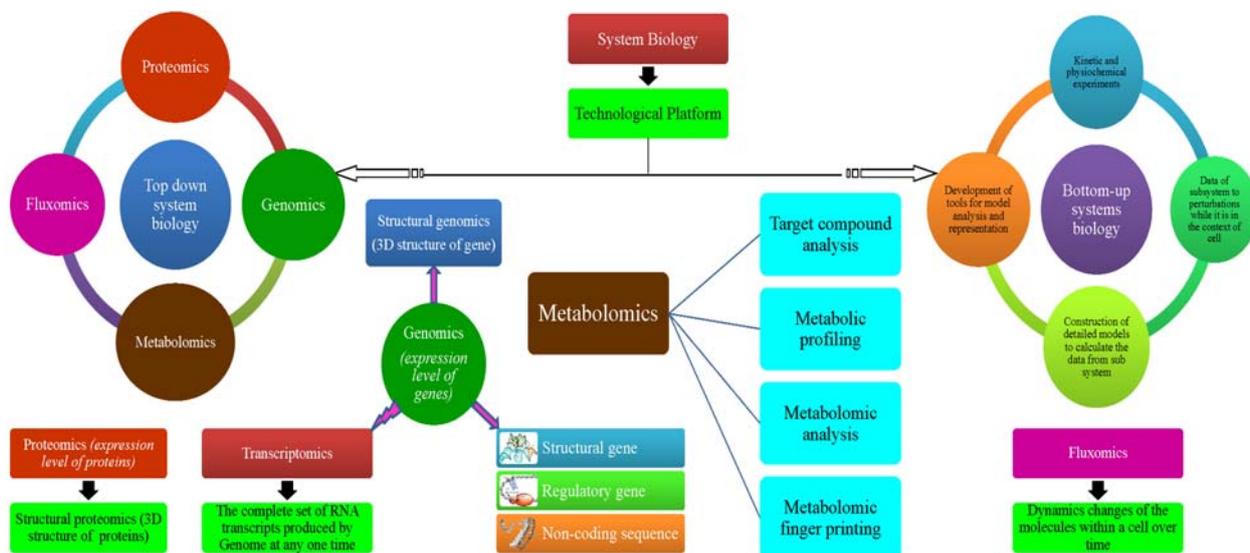


Fig. 4 An overview of system biology in the drug discovery

data are considerably different, which will generally be performed by individuals or in laboratories with different skill sets, and yet necessarily will deal with the same molecules. It is therefore very essential timely to bring together the known or conditional metabolic maps of suitable organisms with measurements of their metabolomes to provide a system level understanding of the metabolic fluxes and metabolite concentration in these organisms, and their way of changing under different conditions (Kell, 2006; Li and Yang, 2008).

“Omic” technologies

The technology like genomics, proteomics, and metabolomics which are high throughput technologies is called “Omic” technologies. Proteomics is the large scale study of proteins, particularly their structures and functions. The term was coined to create an analogy with genomics. It was revealed by the Human Genome Project that there are fewer protein-coding genes in the human genome than there are proteins in the human proteome (about 22 000 genes *vs* about 400 000 proteins). Proteomics-based approaches, which examine the expressed proteins of a tissue or cell type, complement the genome initiatives and are increasingly being used to answer with more clear explanation of biomedical questions. Proteins are the main functional output, and the genetic code cannot always indicate that proteins are expressed, in what quantity and in what form. For example, posttranslational modifications of proteins, such as phosphorylation or glycosylation, are very important in determining protein function. Examination of the genome alone cannot access the effects of environmental factors or multigenic processes such as ageing or disease (Banks *et al*, 2000).

Various key technologies utilized in proteomics are one- and two-dimensional gel electrophoresis which helps in identifying the relative mass of a protein and its isoelectric point (Williams, Coxhead, and Mathers, 2003). Protein-protein or protein-DNA interactions is identified by affinity chromatography, fluorescence resonance energy transfer and surface plasmon resonance. X-ray technology is used to determine the location of proteins or protein complexes in labeled cells. Further, fluorescent proteins like green fluorescent protein (FP), yellow FP, cyan FP or red FP are frequently used to study cellular events such as localization of proteins to membranes and to cellular

organelles. They can mark homogenous populations of specialized cells whose gene expression profiles should be determined by DNA microarray analysis. FPs like green FP are regularly used as straight transcriptional and translational reporters in living cells in a way linking transcriptomics and proteomics (Ulrich-Merzenich, 2007).

The application of this genomics already revealed that gene expression profiles induced by single drugs and the ones induced by the combination of the same drugs may be entirely different. These results make the information of the mode of action of isolated “active principles/lead substances” of phytopreparations questionable. The application of the ‘omic’ technologies may lead to a change of paradigms towards the application of complex mixtures in medicine and open the new field of phyto-genomics, proteomics, and metabolomics.

Metabolomics

Metabolomics aims at qualitatively and quantitatively determining as many compounds as possible in an organism. This can be in extracts of tissues, but also in body fluids such as serum or urine in case of humans. Chromatographic methods in combination with MS, MS with nuclear magnetic resonance spectrometry (MS-NMR) are all used for such analyses. By combining the result of such analyses with other parameters novel correlations can be found, for example a relationship between the occurrence of certain compounds in extracts and a biological activity (Hood and Perlmutter, 2004; Lindon, Nicholson, and Wilson, 2000). Analysis of metabolites in urine by means of ¹H-NMR is already extensively applied for studying toxicity of drugs (Holmes *et al*, 2000). Also for the quality control of botanicals, metabolomics approach is a very promising tool. A study applied with metabolic profiling by means of ¹H-NMR in the quality control of *Ginkgo biloba* L. pharmaceutical preparations. Besides a recognizable pattern, the quantitative analysis of ginkgolides and bilobalide could be done with a 5 min acquisition time of the spectrum, without the need of any elaborate sample preparation (Choi *et al*, 2003). Also for other preparations it was found this method is very suitable, among others preparations studied were strychnos (Frederich, Choi, and Verpoorte, 2003), ephedra (Kim *et al*, 2005), and cannabis (Choi *et al*, 2004). Such studies

are the first step on a long way to a better understanding for the activity of medicinal plants. Because of the many years of documented use, one may start immediately from clinical trials, in that way also shortening the whole process of developing a novel drug. But with some 40 000 to 70 000 plants being used one can see that this will be an enormous task.

Pharmacogenomics

Novel functional genomics and proteomics approaches provide alternate perspectives on the mechanism of TCM action. The target molecules on which TCM either activates or inactivates can be identified by functional genomics and proteomics, thus the affected critical signaling pathway cascades leading to effective recovery of chronic diseases can be studied. Pharmacogenomics utilizes the advantage of genomic techniques such as high throughput DNA sequencing, gene mapping, and bioinformatics to identify the actual genetic basis of interindividual and interracial variation in drug efficacy and metabolism (Mancinelli, Cronin, and Sadée, 2000).

Nutrigenomics

To nourish our body cells nutrition including vitamins, minerals, water, carbohydrates, protein, and fats is mandatory. Nutritious food keeps the normal body system healthy and free of disease, psychological, and behavior issues. The importance of nutrition deals with the relationship between our diet and our body functions. Nowadays, it is recognized that understanding the effect of diet on health requires the study on the mechanisms of nutrients and other bioactive food constituents at the molecular level. This is supported by the increasingly growing number of studies in humans, animals, and cell cultures demonstrating that nutrients and other bioactive compounds in food can regulate gene expression in diverse ways. Nutrigenomics is a new field of research that examines how diet affects gene expression across an individual's entire genome.

Nutrigenetics is an overlapping field that focuses on individual genes, rather than the entire genome, and how they relate to dietary requirements. Phytochemicals of nutritional value are abundant in herbs, fruits, and vegetables. The essential quantity of nutrition acquired by the cells has a very powerful impact on health issues. For example, quercetin functions like an

antihistamine and as an anti-inflammatory effect. Resveratrol, found in grape fruit skins and seeds, is a powerful antioxidant. Thus nutrition plays a powerful role in revitalizing the human body. In order to exploit the nutritional qualities of TM and its effect on health, proper knowledge on relationship between the nutrition and food at the molecular level, genetic level is necessary (García-Cañas *et al.*, 2009).

The field of nutrigenomics seeks to identify the changes in gene expression that are elicited by nutrients. These changes are measured and analyzed and may then be used to determine how susceptible an individual is to certain diseases. More specifically, nutrients and other bioactive food constituents have been referred to as signals that are detected by cellular sensor systems and affect the expression of the genome at several levels (mRNA and proteins) and subsequently, the production of metabolites. These aspects have motivated current trends in nutrition research to study how diet affects the balance between health and disease by altering the expression of an individual's genetic makeup (nutrigenomics) (Chadwick, 2004). Hence the priority of this field is to explore the dietary constituents related to disease risk reduction, prevention, and treatment, and understanding the role of genes in nutritional requirements. Although the potential social benefits are enormous, nutrigenomics raises some ethical issues concerning genetic testing and the potential high cost of new highly personalized functional foods.

Synergy research

Synergy research is a new and novel approach to phytomedicinal research. Synergistic effects, understood as true over additive effects, are often observed in experimental and clinical studies using phytopharmaceuticals (Wagner, 2009). The successful use of herbal drug combinations in TM makes it mandatory to find a rationale for the therapeutic superiority in comparison to the isolated single constituents. Synergistic effects are usually preferred and can be produced if the constituents of an extract affect variable targets in order to improve the solubility and thereby enhance the bioavailability of one or several substances of an extract. For example, a special synergy effect can occur when antibiotics are combined with an agent that antagonizes bacterial resistance mechanisms. The

verification of real synergy effects can be achieved through detailed pharmacological investigations and by means of controlled clinical studies performed in comparison with synthetic reference drugs. Several new ongoing projects aim at the development of a new generation of phytopharmaceuticals which can be used alone or in combination with synthetic drugs or antibiotics (Wagner and Ulrich-Merzenich, 2009).

The introduction of the “omic” technologies is now opening new perspectives in rationalizing these effects and making use of them in the development of phytopharmaceuticals for therapy. Modern medical therapy has acknowledged for quite some time the usefulness of combination therapies in the treatment of multifactorial diseases like cancer, cardiovascular or rheumatic diseases. A systematic exploitation of synergy effects of phytomedical interventions alone or in combination with synthetic drugs should lead in a long term perspective to the discovery and development of more rational evidence-based interventions in the prevention and therapy of multifactorial diseases and thereby enrich modern pharmacotherapy (Ulrich-Merzenich, 2009). Synergistic interactions are of vital importance in phytomedicines, to explain difficulties in always isolating a single active ingredient, and explain the efficacy of apparently low doses of active constituents in a herbal product. This concept, that a whole or partially purified extract of a plant offers advantages over a single isolated ingredient, also underpins the philosophy of herbal medicine. Synergistic interactions are documented for constituents within a total extract of a single herb, as well as among different herbs in a formulation.

Discussion and conclusion

In many parts of the world, conventional medicines are not readily available or affordable to majority of the consumers and the public continue to rely on medicines used traditionally in their cultures. There has been an increased focus in this area by the governments of individual country based on the quality, safety, reliability, and beneficial therapeutic outcomes from the healthcare choices made by the public at large. Accordingly, these social reforms have been matched in the present situation by a growing trend of TM research. It is timely taken issue, because there is now un-

precedented interest throughout the world in bringing to light the molecular basis of the TM biological activities used for centuries and in some cases for thousands of years especially in China and India.

The development of “Omic” technologies has given extraordinary chances to acknowledge our understanding and the use of TM related to their biochemical, molecular, and cellular mechanisms that underlie the beneficial or adverse effects of certain bioactive plant components and related parameters. Similarly to develop a drug from conception to commercialization, the biotechnology and biopharmaceutical industries have reached out and established global strategic partnerships with numerous companies. TM systems such as the Indian and Chinese as well as those used by African tribes are the treasure houses of traditional wisdom, and with the help of modern scientific methods and models, they will continue to be the basis of development of new therapeutic agents globally. Not surprisingly, the medicinal plant based business is flourishing at a dramatic pace. Medicinal plant represents a unique opportunity for interdisciplinary research and it is a thought of our research group who strongly believes that extensive research through collaboration and cooperation can help to a high extent in the promotion and development of the TM, so much so the healthcare globally.

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