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Present scenario, challenges and future perspectives in plant based medicine development

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Abstract

The flora of India remains to be explored and documented to a substantial extent. Pharmaceutical potential of only a small fraction of the plant species has been studied in spite of the existence of vast traditional knowledge on medicinal use, taxonomical clues and the advancement in throughput screening for specific bioactivities. Medicinal plant research should be focused on to produce useful healthcare products (phytomedicines/ nutraceuticals/ food supplements/ conventional drugs) from medicinal and food plants for human welfare. Herbal drugs should be commercially viable and internationally acceptable in light of modern medical sciences. Development of such phytomedicines based on ethnomedical leads is relatively more easy and relevant to our economic conditions, compared to pure chemical entity drug development. Mission oriented multidisciplinary team is required for the development of medicines from plants. Herbal drug research and production of useful healthcare products from locally available plants will lead to improvement in healthcare and economic progress including establishment of herbal drug based industries. Production of good quality plant raw materials (through appropriate cultivation methods and/or biotechnological intervention) and development of commercially successful plant based healthcare products will substantially contribute towards multidimensional socioeconomic progress.

Key words : Medicinal plants, nutraceuticals, phytomedicine, polyherbal formulation

1. Introduction

The use of plants as a primary source of medicines can be traced back to early civilizations of the world. India is one of the biodiversity rich countries in the world with about 46,000 recorded plant species. Plants contain a fascinating array of natural products with varying levels of bioactivities. In India, traditional systems of medicine such as Ayurveda and Siddha use about 1200 plants for medicinal purposes. In local health traditions including tribal medicines, about 7500 plant species are used (Pushpangadan, 1995). About 5000 species of higher plants have been investigated globally as potential sources of new drugs, and over 125 chemical compounds (drugs) were isolated in pure form from nearly 90 plant species (Beigh *et al*., 2002). Many of the medicines in current use have been derived from traditional medicinal plants. In conventional Western medicine, 50-60 % of phamaceutical commodities contain natural products or synthetic natural products.

Plants continue to provide new medicines and new lead molecules for the development of drugs against various diseases (Jachak and Saklani, 2007). Even today, plants remain as a major source of medicines for human healthcare, particularly in rural areas. Traditional knowledge and medicinal plant diversity are very important for multifarious novel healthcare product development in light of modern science.

It is estimated that around 1.25 lakhs flowering plants occur in the tropical regions of the world and only about 1-2 % of tropical plant species have been studied for pharmaceutical potential (Jachak and Saklani, 2007). Herbs used in tradicinal and folk medicines, constitute only a small portion of naturally occurring plants. Almost all plants on earth may have pharmacological properties. The recent discovery of promising anti-inflammatory activity in chlorophyll-a and its degradation products shows that all chlorophyll-a bearing plants have pharmaceutical potential (Subramoniam *et al*., 2012). It is possible that very attractive and beautiful flowers may have unbelievable pharmacological properties. For example, a new compound, 2,7,7-trimethyl bicyclo [2.2.1] heptane, which selectively activates endothelial and neuronal nitric oxide synthase has been isolated from a beautiful orchid flower (Subramoniam *et al*., 2013).

Efficient use of all available data and creation of new data on the therapeutic potential of medicinal plants and phytochemicals are important factors for developing new and desperately needed products for human healthcare and the success of pharmaceutical companies. This review attempts to give glimpses of present scenario of medicine development from plants and to give insights on the perspectives of medicinal plant research and production of valuable medicines.

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2. Present scenario

In India, in the last one and a half decade, there is an increasing awareness towards herbal drugs and medicinal plants. This has resulted in an increase in funding for research; new departments such as herbal science department, even new herbal institutes are established and are emerging. There is a marked increase in publications and most of them are mediocre and a good percentage of papers published in relatively low standard journals are repetition to a considerable extent. Unfortunately, to a large extent, internationally acceptable and commercially viable new phytomedicines or plant based conventional chemical entity medicines are not developed. The world market for safe and effective phytomedicine is 60-100 billion US $ where India's share is 0.1 billion $.

Recently, many of the reputed pharmaceutical companies have started producing a number of herbal preparations. The demand for quality raw materials has increased considerably. The medicinal plants based industry is growing at the rate of 7-15 % annually. Recent records on herbal medicine market are not available. The herbal medicine market in 1991 in Germany, France and Italy was $ 3.0, 1.6 and 0.6 billion, respectively. In Germany and France, herbal extracts are sold as prescription drugs. In 1996, the herbal medicine market in USA was about $ 4 billion and that for Europe was about $ 10 billion. The local Indian market in 1996 was about $ 1 billion, but the export of herbal crude extract was only $ 0.08 billion.

Estimated global imports of raw medicinal and aromatic plants and plant parts in the year 2001 exceeded a billion US dollars. India being the second largest exporter, next to China, of raw medicinal plant materials, accounted for about 13 % of global imports. The domestic market for medicinal plants or related products is about Rs. 4000 crores. This along with as export level of Rs. 1200 crores makes the commercialization of Indian medicinal plant sector at Rs. 5200 crores.

Among the developed countries, on herbal drug research, Germany is the most active country. It has published individual monographs on the therapeutic benefits of more than 300 plants. In developing countries, China has generated sufficient data on more than 800 medicinal plants and is exporting large amount of herbal drugs. India has prepared only some monographs and its herbal drug exports are minimal (Kamboj, 2000). In China, there are 187518 kinds of home manufactured drugs and 1489 patent protected products of traditional herbal medicines (Pan *et al*., 2013). Unlike China, India has not been able to capitalize on the traditional knowledge on herbal medicine by promoting its use in the developed world despite the renewed interest in herbal medicines.

Although most of the medicines used in traditional systems of medicine such as Ayurveda, Siddha and Unani are believed to be time tested, in most of the cases, standards of safety, efficacy and authenticity are lacking when viewed in light of modern science. Mechanisms of actions of these medicines are also not fully understood as per modern biology and medicine. Expiry dates, based on experimental evidences, are not fixed for these medicines. China has rejuvenated its traditional medicine to a large extent with modern standards of safety and efficacy, resulting in huge commercial benefits from global market.

In the area of conventional chemical entity drug research, as reported in 2003, 61 % of 877 chemical entities introduced as drugs worldwide during 1981-2002, were inspired by natural products (Newman *et al*., 2003). During the period 1981 to 2006, 47.1 % of a total of 155 clinically approved anticancer drugs were derived from nature in North America, Europe and Japan market (Pan *et al*., 2013). India did not contribute much in this area. Drugs like guggulsterone (hypolipidemic drug isolated from *Commiphora mukul*) and forskolin (isolated from *Coleus forskohlii*) were discovered from Indian traditional plants based on traditional medicinal use in India. Although the antihyperlipidemic and other activities of *C. mukul* was shown by Indian researchers (Satyavati, 1988), the mechanism of action of guggul sterone (farnesoid X receptor antagonist action) was discovered by foreign investigators (Urizar *et al*., 2002). The mechanism of action of forskolin (a labdone diterpenoid) is inhibition of cyclic AMP. A semi synthelic deribative of forskoolin was approved for treatment of glaucoma in USA.

Due to very limited number of taxonomist available, inaccessibility of some of the wild terrains and forests and above all insufficient efforts taken by the government, about 35% of plants occurring in India have not been surveyed, identified and documented. We have approximately 17500 species of flowering plants and out of this, 5725 are recorded as endemic. According to government of India notification, the export of 29 rare and endangered taxa has been banned; these and red listed threatened species cannot be collected from the wild (Jachak and Saklani, 2007). Therefore, there is a need to conserve and propagate these plants for determining their pharmaceutical potential.

Meaningful agrotechnology was not developed to almost all medicinal plants. Most of the medicinal plants are collected from the wild even today. This gradually leads to inaccessibility to medicinal plants, species extermination due to indiscriminate collection, forest destruction, mixing of genuine plants with spurious materials, *etc*. Authentication of botanical identity of drugs is also a problem in some cases.

Although we have rich flora, hardly a few Institutions like CDRI, Lucknow could test considerable number of plants and have published results on 3488 species of plants for limited indications between 1968 and 1996. This resulted into some promising leads. The medicines developed include bacoside, the memory enhancer (Promind) from *Bacopa monnieri*; Picroliv, the hepatoprotective medicine from *Picrorhiza kurroa*; Centchroman (Saheli) a safe and effective non-steroidal oral contraceptive for women; and Consap, the contraceptive cream from *Sapindus mukorossi*. Other CSIR laboratories and some private pharmaceutical companies have also made some efforts towards medicine development from plants.

Other plant-derived medicines developed by CSIR institutes include Arteether (E-mal), a blood schizontocidal antimalarial; Elubaquine (Aablaquin), an antimalarial effective against *Plasmodium vivax*; Asmon, a polyherbal standardized drug for asthma; Sallaki, an anti-inflammatory drug for the treatment of rheumatoid arthritis and osteoarthritis produced from *Boswellia serrata*; Livzon, a multiherbal formulation with hepatoprotective properties; and Immines, a multiherbal formulation with immune-modulatory properties. These are developed over a period of more than 2 decades. Further, international acceptability and commercial viability of these drugs are questionable.

In the national scenario, industries such as SPIC Pharma, Chennai; Dr Reddy's Foundation, Hyderabad; Ranbaxy Laboratories Ltd, Gurgaon; Dabur Research Foundation, Ghaziabad; Zanda Pharmaceuticals Work Ltd, Mumbai; Recon Ltd, Bangalore; Bharat Biotech International Ltd, Hyderabad; Cadila Health Care Ltd, Ahmedabad; Indian Herbs Research and Supply Company Ltd, Saharanpur; Glenmark Pharmaceuticals Ltd, Mumbai; Alembic Ltd, Vadodara; Lupin Laboratories, Mumbai; Dey's Medical Stores Mfg., Ltd, Kolkata and Herbochemical Remedies India (P) Ltd, West Bengal have undertaken research and development activities in collaboration with national institutions for the development of healthcare products. Some of the Ayurvedic companies are also attempting to develop standardized phytomedicines.

Agencies of government of India like Department of Biotechnology, Council of Scientific and Industrial Research (CSIR) and Department of AYUSH, Ministry of health and Family Welfare have initiated efforts on bioprospecting of medicinal and aromatic plants. CSIR has started a co-ordinated programme on drug discovery with a net work of 19 CSIR laboratories and other Institutions and Universities working in the field of traditional medicines. The Planning Commission of India sponsored the New Millennium Indian Technology Leadership Initiative (NMITLI), one of the most innovative bioprospecting programmes. To a large extent, these initiatives have not yet provided the anticipated outcomes or deliverables. I feel there is a need to augment the implementation part of these initiatives.

According to 'The Biological Diversity Rules, 2003' of the Government of India, any person who is not a citizen of India or any foreign corporate should get the approval of National Biodiversity Authority (NBA) for access to biological resources and associated knowledge for research or commercial utilization. However, a citizen of India need not seek permission for the access of wild biodiversity for use in India; respective state biodiversity board may be informed for collection of plant materials.

3. Challenges in plant based medicine development

When ethnobotanical approach is utilized for drug discovery, information sharing with the traditional knowledge holder is involved. It is necessary to honour the intellectual property rights of a given cultural group or tribes or local people of a country where plants are collected based on their ethnomedical knowledge (Baker, 1995). Here, informed consent, recognition of Indigenous Intellectual Property Rights as well as short and long term benefits sharing need to be taken care of.

Presence of several pharmacological properties in one plant is observed in most of the cases. Experimental studies have to be done to identify therapeutically valuable properties from other properties. Another problem is toxicity associated with beneficial properties. In these cases, if the toxic molecules are different from medicinally important molecules, toxic molecules may be separated from the active extract or fraction using suitable isolation procedures. Further, in phytomedicine development ecotype and genotype variations in efficacy and safety are problems. This requires an extensive research plan, because the pharmacological activities (the amount of bioactive compounds) in a plant species varies with so many factors such as soil characteristics, agroclimatic conditions of the habitat, plant genotype, plant parts, stage of plant development, nitrogen-use efficiency of the plant, association of microorganisms like specific bacteria and fungi and the level of environmental pollution (Iqbal *et al.,* 2011). The suitable ecotype and genotype has to be selected based on scientific studies.

Standardization of techniques for cultivation of medicinal plants is very essential. This should include impact of environmental changes on the active ingredients. In most of the cases, the active ingredients are not identified. In those cases, there is a need to use pharmacological standardization to establish medicinal quality of the plants (Subramoniam, 2003a). Although elucidation of marker compounds has a key role in the standardization of herbal medicine, medicinal value of a plant cannot be established based on marker compounds alone because in many cases the marker compounds are not the major active molecules and the relative amounts of the bioactive compounds may differ due to so many factors.

Numerous plants with widely varying degrees of the same therapeutic action are occurring. For example, in India more than 100 plants are reported to have antidiabetes and/or hypoglycemic property (Ajikumarannair and Subramoniam, 2005). In such cases, potential plants have to be compared for efficacy and safety and the most promising plants are to be used for further studies aimed at medicine development.

Some of the bioactive compounds are soluble in highly polar solvents. The conventional methods used by phytochemists to de-fat the dried plant material with petroleum ether extraction *etc*., may lead to loss of the active compounds. This has to be overcome with initial extraction with solvents like hexane or petroleum ether and testing the bioactivity of extracts. Development of suitable dosage forms or drug delivery systems for sticky, insoluble extracts and fractions is a hindrance.

In some cases, one of the important aspects is lack of sufficient amount of good quality plant materials. Once found active in the preliminary screening, target plant collection in bulk quantity may be a problem due to limited availability of plant-mass, scattered distribution, *etc*.

Authentication of plant species is difficult in some cases; this is particularly true and most crucial in the case of lower plants such as bryophytes, fungi and algae. Unfortunately, expertise in taxonomy is on the decline.

4. Future perspectives

4.1 Promising areas of research

Promising areas of research for phytomedicine development and for new chemical entity drug development from plants include infectious diseases (particularly viral diseases such as HIV), arthritis, liver diseases, diabetes, cancer, age-related diseases (*e.g*., memory loss, osteoporosis and immune disorders), hypertension, sexual dysfunction and hyperlipidemia.

In recent years, many plant-derived antiviral compounds have been formally licensed; more than a half of these are for use in the treatment of human immune-deficiency virus (HIV) infections (AIDS). Others have been licensed for the treatment of infections with viruses such as herpes virus, hepatitis B & C and influenza. For other viral infections such as poxviruses (variola, vaccinia),

hemorrhagic fever virus, picorna virus, flavivirus, pappiloma virus and adenovirus, effective antiviral drugs remain to be developed.

Besides, natural products have major roles in the discovery of novel antibacterial and antifungal agents. For example, chemical diversity of polyketides and glycopeptides has imparted unique antibacterial activities against multiple organisms. Tygacil (Tigecyclin, GAR-936) is an example of this type of antibiotics. Discovery of novel drugs against tuberculosis and malaria is also promising. Malaria causes about 0.9 million deaths each year in Africa (Pan *et al*., 2013).

In the case of cancer, (in addition to the existing plant derived chemotherapeutic agents), novel chemopreventive and therapeutic agents can be developed with minimal side effects. In this area, plant-derived phytochemicals raise high expectations, since unwanted side effects are relatively low.

4.2 Nutraceuticals

Nutraceuticals are plant products with nutritional and medicinal value. In other words, these are food (ingredients of diet) with pharmaceutical properties (bioactivities). Nutraceuticals have health benefits when consumed to the optimum levels. The term 'nutraceuticals' emerged in 1979 (Brower, 1998). Spices such as turmeric and garlic, vegetables like bitter gourd, fruits like grapes and papaya, rice bran and goose berry are examples of nutraceuticals. These ingredients of food have biologically active molecules also. For example, curcumin from turmeric have antioxidant, anti-inflammatory and cancer preventive properties when consumed at reasonable levels. Too much could be harmful. Similarly sulfur compounds in garlic extract have hypolipidemic property. Grapes, pea nuts *etc*. can be considered as nutracuticals because they contain, among other things, pharmacologically active reserveratal. Lycopene from tomatoes is belived to prevent certain types of cancer. Herbal drugs which are not edible (not ingredients of diet) are not nutraceuticals. Many pharma and biotech companies erroneously extended the term nutraceutical even to isolated compounds from wild plants which are not ingredients of diet (Kamboj, 2000). For example, docosohexaenoic acid, a cardiovascular stimulant, from algae is marked as nutraceuticals. Many herbal preparations are being marked as nutraceuticals without following the minimum standards laid down by WHO to herbal drugs (WHO, 1991). This is a dangerous trend considering human health. The Dietary Supplement Health Education Act passed by USA in 1994 permits unprecedented claims to be made about food or dietary supplements' health benefits. In view of this, unfortunately, many herbal remedies and isolated compounds are marked as nutraceuticals by some of the pharma companies. The regulatory agents should stop this dangerous trend as was done by US-FAD by banning the so called dietary supplement cholestin (lavastatin).

Nutraceuticals are in great demand, considering their safety and health benefits, particularly, in the developed world. Nutraceutical market in USA alone is about $ 80-250 billion (Brower, 1998). Recent reports on sales of nutraceuticals are not available. It may be about 40 times higher. Nutraceuticals do not involve regulatory clearances and offers large market and health promotion role. India can produce health enhancing and protective nutraceuticals and food supplements in a big way.

4.3 An integrated approach to drug development

Development of phytomedicines and plant based chemical entity medicines requires a concerted co-operation and efforts between botanists/ plant taxanomists, phytochemists, molecular biologists/ biochemists, pharmacologists and clinicians with the aim to integrate new molecular biological assays into the screening of plant extracts and plant constituents, to use modern hightech methods for the standardization of phytopreparations, to determine the mechanisms of actions of phytopreparations, to evaluate safety and efficacy in experimental animal models and to perform controlled clinical trials and bioavailability studies (Wagner, 2004; Subramoniam, 2003b). When drugs are being developed from plants, based on ethnomedical leads, ethnobotanists and traditional doctors may also be involved in the mission oriented team work. In chemical entity drug discovery, phytochemists and pharmacologists work together to isolate and characterize the active compounds through bioassay guided isolation. Molecular-biologists and biochemists are essential to set up appropriate assays directed to physiologically relevant molecular targets and discover mechanism of action. To a large extent, such a concerted multidisciplinary term is not involved in herbal drug development in India to a large extent. This could be one of the major reasons for the lack of production of new phytomedicines with international acceptability. In India, such a facility may be available only in a few institutes like Central Drug Research Institute, Lucknow. For good quality plant materials, agrotechnology or cultivation methods should be developed where agricultural experts/ agrotechnologists should work hand-in-hand with phytopharmacologists and phytochemists. Biomedicine should dissolve gradually the long standing barrier between the synthetic drugs and natural drugs including polyherbal therapies.

4.4 Polyherbal formulations and combination therapies

Polyherbal formulations can be better than single chemical entity drugs in many medical conditions. The multivalent and multitarget actions of mixtures of phytochemicals and standardized extracts could provide therapeutic superiority compared to single compound drugs.

Now, it is increasingly recognized that, in most disease conditions (*e.g.,* arthritis, liver diseases, radiation induced injuries, old age related diseases and diabetes mellitus), combination therapy is more suitable compared to monosubstance therapy. It is considered that complex physiological processes of the body can be influenced more effectively with less adverse side effects by a combination of several low dose compounds than by a single high dose compound. Low doses of several active phytochemicals acting on multiple targets involved in a complex disease may prove better and safer compared to a high dose of a pure chemical entity drug acting on a major target. This gives relevance to phytomedicines (generally containing standardized extracts/fractions/polyherbal combinations); phytomedicine is easy to develop compared to conventional pure chemical entity drug.

In the case of virus-induced liver damages, several pharmacological activities such as antihepatitis viral activity, antioxidant activity, stimulation of hepatocyte regeneration, stimulation of bile flow *etc*. are required for superior healing effect (Subramoniam and Pushpangadan, 1999).

For rheumatoid arthritis, the polyherbal phytomedicine should contain at least one ingredient to suppress the underlying hyper immune reactions (including high levels of certain cytokines) in addition to safe and effective anti-inflammatory and analgesic agents. Agents which protect chondrocyte function and prevent cartilage degradation and bone erosion may be needed. Matrix metallo protease (MMP) catalyzed cartilage degradation can be counteracted by MMP inhibitors (Subramoniam *et al.,* 2013). It is beneficial to have antioxidants also; oxidative stress and free radical accumulation are seen in arthritic patients. Antihyperlipidemic extract or fraction is also required in the case of hyperlipidemic arthritic patients. Suitably prepared polyherbal formulations may provide all these actions. Experiments have shown that in the case of rheumatoid arthritis, combinations of IL-1 receptor antagonists and methotrexate could achieve superior efficacy at lower doses compared with either agent alone at relatively higher doses (Bendele *et al*., 1999). Both the agents are toxic at higher doses. There are many examples like this. Most of the required activity may not be provided by a single chemical entity in a given disease condition. However, many drugs, particularly those derived from natural products hit multiple targets, each of which exists within a complex net work. Approximately 35 % of known drugs or drug candidates are active against more than 1 targets (Pan *et al*., 2013). For example, curcumin, a polyphenol natural product isolated from the rhizome of *Curcuma longa* has several molecular targets. Curcumin shows anticancer, antiviral, antiarthritis, antiamyloid, antioxidant and anti-inflammatory properties. However, a variety of drug targets may not give advantage in clinical trials against a specific disease condition (Pan *et al*., 2013). This may be due to the need for relatively high concentrations to act on more important targts; high dose may develop toxicity. Further, the drugs may have unknown unwanted targets also.

Numerous polyherbal formulations are used in traditional medicine; these are used from time immemorial. The reason behind the inclusion of each ingredient of the formulation in the said ratio is not clear. These are not scientifically developed polyherbal formulations; empirical knowledge may have a major place in the origin of these formulations. The development of rational polyherbal formulations requires a lot of pharmacological and toxicological studies and phytochemical standardization. For example, in the development of a polyherbal formulation, using active extract/ fraction/compound from 3 herbs (Herb 1, 2 and 3) first pharmacological evaluation of each plant has to be carried out, using 3 or 4 reasonable doses; if active the optimum dose may be fixed in each case. Then, combinations of 2 plants (1+2, 2+3 and 1+3) in different ratios (generally optimum dose in each case and lower than that) have to be evaluated. Finally, the combinations with the 3 plants (1 + 2 + 3) in different rations are to be done. The safety study (toxicological evaluation) for the most promising combinations should be carried out. When the number of plant ingredients in the combination increases, the work to be carried out increases tremendously when various permutations are considered.

4.5 Development of pure chemical entity drugs

Herbal drug research can be directed to the following:

- Finding new plant sources for already known plant derived drugs.
- Genetic manipulation of the biosynthetic pathways of high value natural product drugs to increase drug production.
- Search for and discovery of specific inhibitors and/or activators of key enzymes and receptors. This is not only useful for the mechanism based discovery of novel drugs for pharmaceutical industry, but also useful to discover research tools.
- Discovering new natural product drugs/pharmacophores/lead molecules by pharmacological screening.

Pharmacological and phytochemical prospecting of medicinal plants (selected based on traditional knowledge) can lead to the discovery of new pharmacologically important activities not mentioned in traditional use. For example, studies carried out at Tropical Botanic Garden and Research Institute (TBGRI) on *Hemidesmus indicus* root led to the isolation of water and electrolyte absorption enhancing activity in the water extract of the root (Evans *et al*., 2004). Follow up studies led to the isolation of active principle and improving the ORS (oral rehydration salts) used to save children suffering from diarrhoea and vomiting, particularly, in remote villages. This herbal medicine awaits clinical trial (Patent filed).

Development of a new chemical entity drug from plant products is tedious, time consuming, expensive and risky. In 2004, the process of modern chemical entity drug discovery has been estimated to take an average period of 10 years and cost more than 800 hundred million US dollars (Dickson and Gagnon, 2004). In 2006, it has been estimated to take, on an average, about 10-15 years for a newly synthesised drug to become a marketable therapeutic agent and the cost was approximately 1 billion (Pan *et al*., 2013). Now, the cost would have increased substantially. It is estimated that only one in 5000 lead compounds will end up as a successful medicine. However, a successful drug can bring billions of dollars and associated industrial activity. Generally, the success rate of the synthetic route for developing new medicinal agents may be 1 in 10000; however, the success rate with search for new therapeutic moites based on medicinal plants used in traditional medicine for a long time can be as high as 1 in 4 compounds (Pan *et al*., 2013).

Natural products continue to serve as excellent leads for the discovery and development of new drugs and at the same time, provide both synthetic challenges for organic chemists. Drug discovery/design has relied very heavily on structural computational chemistry in identifying novel drug compounds, optimizing lead compounds for specific therapeutic targets and in assisting experimental R&D programs in bringing potential drugs to the market. One of the most important computational chemistry tools to predict the bound conformation of a small molecule to a macromolecular target is molecular docking.

Unfortunately, this highly interdisciplinary nature of medicinal chemistry, as well as the numerous new technological advances aimed to help the medicinal chemist to more rapidly access drug like compounds, did actually not increase the number of new drugs which has fallen steadily during the past several years. This actually happens mainly because of a lack of proven efficacy and unexpected toxicological side effects that compounds show in late stage clinical trials.

4.6 Toxicity evaluation in animals

Since time tested, traditional medicinal plants are used for a long time without any known or recorded toxicity, normally the LD_{50} values are extremely high (5 to 10 grams or even more than that for kilogram body weight). Therefore, LD_{50} value determination is not required for well known medicinal plants when they are used as

crude water suspensions, decoctions, extracts, *etc*. An acute toxicity study with reasonably high doses is sufficient. WHO has also recommended for the same. In practical purposes, a reasonably high dose for pharmacological studies could be 500 mg/kg (dry weight) for *in vivo* studies and 1 mg/ml for *in vitro* studies. However, toxic drugs like those used for chemotherapy for cancer, LD_{50} should be used for dose fixation.

4.7 *In vitro* propagation and cultivation of medicinal plants

There is an urgent need to develop agrotechnology for high value medicinal plants for providing quality raw materials for the preparation of plant based drugs. Currently, there are 250 kinds of medicinal plants being cultivated in China, encomposing 33.3 million hectares of farm land (Pan *et al*., 2013). In the long run, there is a need to cultivate required medicinal plants under specific growth conditions, to maintain medicinal value. There is a need to develop suitable conventional cultivation techniques or agrotechnology to each high value medicinal plants. For optimization of medicinal value, the development of agrotechniques should be linked to pharmacological and phytochemical evaluation. Determining suitable cultivation techniques should not be limited to the production of optimum biomass, but it should take care of phytochemical profile. Since in most of the medicinal plants, fuller information on the active principles and toxic compounds, if any, is not available pharmacological standardization is required. In the case of important medicinal plants which are not amenable for rapid propagation by conventional cultivation methods, biotechnological intervention is needed to get desired quantity and quality of plant biomass. This may be achieved by developing *in vitro* propagation techniques including *in vitro* tissue/cell culture and production of high quality seeding materials through *in vitro* techniques.

Conflict of interest

I declare that I have no conflict of interest.

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