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Review Article

CHANGING LANDSCAPE OF HERBAL MEDICINE: TECHNOLOGY ATTRIBUTING RENAISSANCE

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ABSTRACT

Herbal medicine is undoubtedly the oldest system of medical science in the world. Utilization of nature's wealth for health benefits and the cure, prevention and mitigation of diseases plays a big role in human civilization, with a dependency of a large number of human populations particularly in developing countries. Globalization of the local knowledge regarding the use of indigenous medicinal plants by traditional healers and localization of globally advanced technologies have boosted the growth of herbal industry and created immense global interest towards herbal medicine. The advancement in the technologies have also helped the developed countries to adopt this ancient and enriched medicinal system in a new way. An improvement in each step of herbal medicine production has recently been possible with the aid of technical developments. The increase in the demand and utilization of herbal medicine in the past few years has been increased considerably indicating herbal 'renaissance'. The current trend of utilization of these formulas after scientific researches and modern technological aspects helped in industrial growth of herbal medicine.

Keywords: Herbal Medicine.

INTRODUCTION

From the beginning of human civilization people are indebted to nature in many ways. From time immemorial plants and natural products are being used for prevention, mitigation and cure of diseases, which was the advent of primitive healthcare system. The primary health care in most of these ancient civilized societies are based on herb based medicines yet still fuzziness exists in encompassing different domains of herbal medicine as a whole (Figure 1). Contributions from ancient civilizations like Arian, Egyptian, Sumerian, Greek and others towards herbal medicine highlights conglomeration of experimental and occult knowledge specific to a particular culture. Countries like India, China, Japan, Egypt as well as Africa, Pakistan and Middle East, have their own forms of indigenous healthcare systems mostly based on herbs (Table 1). In the last part of twentieth century, Western Nations realized the importance of herbal medicine as the one that possesses maximum health benefits with minimum adverse effects and countries like USA, UK, Australia, and other European countries have accepted the medication [1, 2]. Herbal drugs are recently prepared mostly by eco-friendly processes from plants and can be defined as preparations containing active constituents of medicinal importance. It is also often called as phytomedicine/ botanical and considered as a part of alternative and complementary medicine. The traditional systems of medicine revived in all over the world in the light of modern technological aspects. Advancement in different areas of herbal research starting from extraction procedures to isolation and identification techniques, design and utilization of bio-assay for efficacy testing, dosage form design, and study of pharmacokinetic, pharmacodynamic, toxicological and pharmacological mode of action call for a healthy competition with existing classic health care systems. Simultaneously, uses of forensic studies in regulatory aspects as well as global marketing strategy are other highlighted areas of herbal medicine industry. The literature survey based study addresses these important issues on global perspective.

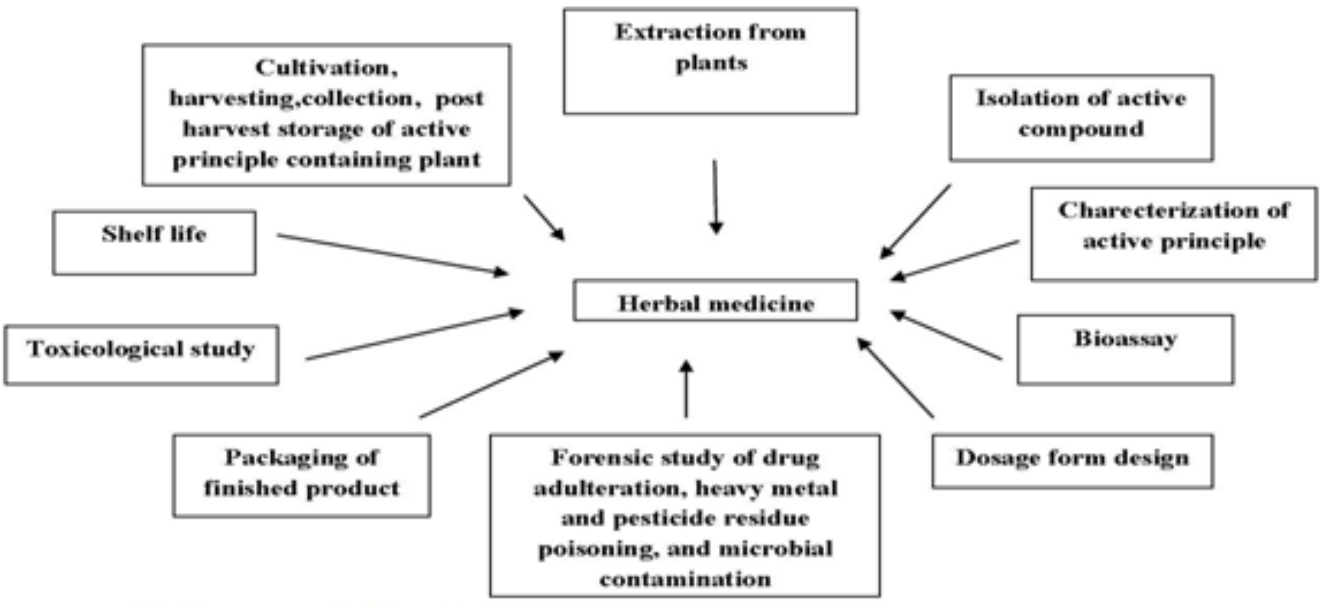

Fig. 1: Different domains of herbal medicine

Table 1: Existing Traditional Medicinal Systems in Different Countries

Country	Traditional system of medicine
India	*Ayurveda, Siddha,*
China	Chinese Herbal medicine
Japan	*Kampo*
Korea	*Hanbang*
Pakistan	*Indusynunic*
Middle east	Islamic, *Unani*
Europe	Aromatherapy, homeopathy, botanicals and herbalism
USA, Australia	Western Herbal medicine
Africa	Many traditional medicine systems used by various tribes like *Muti, Ifá* etc. and made operational by *sangomas* or *izinyangas*, traditional healers etc..

According to W.H.O. herbal medicine is mainstay for 75- 90% people in developing countries for primary care [3]. Its safety, efficacy, biocompatibility, better cultural acceptability, ease of availability and lesser side effects are some of the causes of its increasing acceptance worldwide. The annual growth rate of herbal medicine nowadays is nearly between 5% and 15% with an annual income of US$60 billion. The revenue earned through herbal drugs in some countries are quite impressive as per W.H.O, that, US$5 billion in Western Europe (2003-2004), US$14 billion in China (2005) and US$160 million in Brazil (2007). The global estimate of traditional medicinal market in 2008 was US$83 billion showing an exponential increment [3, 4]. With the developments in technological field and implementation of specific regulatory measures in cultivation, harvesting, and other processes related to medicinal plants researches in the field of herbal medicines flourished resulting to increased awareness towards the adversities in the arena like undesirable effects, drug-drug interactions and increased self medication tendencies etc. Some problems faced today includes the presence of minute quantity of active principle, lack of knowledge regarding dosage calculation due to varied concentration of active constituent from same amount of raw material, lack of standardized procedures for medicament preparation, less awareness to toxicity of herbal drugs, adverse effects and interaction consequences etc. New researches are being carried out to address these aspects. Studies in respect to the systematical revision of the traditional use of wild and cultivated plants; ethnobotanical reviews in mostly all parts of world are very common area of study today. New approaches for novel lead identification from herbal sources during drug discovery are major leap toward globalization of confined local knowledge. Advancements in instruments for better identification, characterization of active principles, in assays to carry out their efficacy studies, increased scope of forensic sciences in the field of herbal drugs indicate the beginning of herbal 'renaissance'.

Cultivation, harvesting, collection, post harvest storage of medicinal plants –

Change in environmental conditions during cultivation or medicinal plant growth, improper agricultural practices followed during cultivation and harvesting, malpractices occurred during drying and improper post harvest storage conditions etc. are some major important but quite neglected area in herbal drug research. Conditioned drying, processing, post harvest storage, production procedures like extraction, final processing before packaging, transportation also affects the secondary metabolite concentration and type [5]. The factors mentioned above can affect composition and yield of active compounds as well as biological activities of medicinal plants [6]. This area is also being given importance nowadays even in poor countries. During each extraction step also, amount of active components in extract may varies. Therefore the extract should then be checked for indicated biological activity in an experimental animal model which is not always possible. One recent study states suggests that if therapeutic index is provided with cultivation success, batch to batch variation of active constituent can be minimized and information about best time of harvest can be known. That study also suggest that cultivation will be more effective for medicinal plants to get better yield with fertilization and irrigation [7]. Good Agricultural Practices for medicinal plants prescribed by WHO India in 2009 were suggested to be followed [8].

Many moulds and toxigenic bacteria are susceptible to grow on herbal raw material as well as during post harvest storage, and often produce toxic compounds due to deterioration. Therefore change in chemical composition often affects the medicinal efficacy of the herbal drugs [9]. Studies have shown that aqueous extract of *Adenocalymma alliaceum* can act as antifungal and antiaflatoxigenic [10]. Ocimum sanctum essential oil (EO) along with Eugenol can be exploited for this purpose [11].

Herbal drug extraction, identification, isolation, characterization and Drug discovery

With the help of genomics, gene manipulation and metabolic engineering techniques it is possible nowadays to develop new drug component from natural origin for developing new herbal drug candidates. Along with these new techniques in search of new drug candidates various pharmaceutical companies are also exploring plants from less investigated areas of world like North and Southeast Asia and Oceania [12].

Drug discovery is mainly done by high throughput screening (HTS), but this approach is becoming less successful due to presence of number of good compounds already available in the market and increasing cost of this method. The research to solve the problem associated with HTS shows high time consumption, nonspecific interference, problems due to fluorescence and insolubility [12]. Therefore again role of traditional herbal formulas are getting importance due to their apparently safe use. In case of theoretical screening of herbs importance of HTS still remains and has been reported in many articles. The process is now used with success for screening of plants for new lead compounds from herbs. The other new technologies includes virtual screening filtering experiments using pharmacophore models, docking studies, and neural networks for novel lead identification from natural product. DNA, protein, and cell chip based HTS are being used today as miniature version of complex HTS method. DNA microarray is useful for pharmacognostic, pharmacogenomic, and pharmacodynamic studies of herbal drugs [13]. Even fluorescence resonance energy transfer (FRET) based High Throughput Screening is being used as a new tool for anti cancer drug designing [14]. Construction of high quality natural product library through high throughput screening is an approach for complexity reduction. One of the other major bottlenecks of natural product drug discovery is numbers of metabolites that are present in natural products and their huge dynamic range which result in the loss of many possibly bio-active natural compounds. This also causes increase in cost of drug by high throughput screening. These problems nowadays are thought to be solved with proper use of metabolomics approach [15] or by use of chromatographic fingerprinting profiling of each medicinal plant.

Similarity search is one of the most efficient methods in cheminformatics methodology to detect specific bio-molecular targets expected to have effects for certain diseases where screening and introduction of novel herbs for particular disease is possible [16].

Extraction of active principle from medicinal plants is one of the critical steps in herbal technology. Method of extraction is mainly aqueous and solvent extraction. Previously extraction was done using the steps like distillation, decoction, maceration, percolation etc. Recently newer modified techniques have been introduced. In 2006, after South-East Asian (SEA) Regional Workshop entitled ˝Extraction Technologies for Medicinal and Aromatic Plants, ˝ held in Lucknow, a new publication solely on newer techniques of extraction were published by International Center for Science and High Technology (ICS). Along with the conventional techniques newer techniques like Micro-distillation, Thermo-micro-distillation and Molecular Distillation Techniques, Solid Phase Micro-extraction and Headspace Trapping Extraction, Super-critical Fluid Extraction, Process-scale HPLC, Flash Chromatography and Low Pressure Chromatography, Counter-current Chromatography, High performance Thin Layer Chromatography (HPTLC) were also mentioned as extraction techniques. These new techniques are tabulated in table 2.

Table 2: Some newer extraction techniques

Some New Extraction Techniques	Uses	Reference
Supercritical Fluid extraction (SFE)	Improved extraction efficiency and pesticide residues analysis is possible	17, 18
Pressurized Liquid Extraction (PLE) and PLE combined with ultrasound-assisted extraction and solid phase extraction	Increased yield and decreased time and solvent consumption and protects sensitive compounds	18,19
Microwave assisted extraction (MAE) technique and different statistical optimization strategies	Extracts can directly used for HPLC	18,20
Ultrasonic extraction	Increased extraction efficiency and reduced extraction time	18, 21

Most important area of study of herbal technology specifies active component isolation and identification followed by study of biological activities. Most of the isolation and identification steps used nowadays are also considered for quality control aspects to detect adulteration simultaneously. Quality control, safety and efficacy study of herbal drug is therefore a major thrust area of research today as drug adulteration is a common and major problem faced by herbal industry. Some technical methods to analyze the active principle as well as adulteration include Thin layer chromatography (TLC), High performance liquid chromatography (HPLC) and capillary electrophoresis (CE) etc. Tandem techniques such as Gas chromatography (GC)/ Mass spectroscopy (MS), Liquid chromatography (LC)/MS and CE/MS are also some measures which provide higher specificity and these are mostly used for confirmation studies. Liquid chromatography-selected reaction monitoring mass spectrometry (LC-SRM/MS) is a new technique. Techniques to analyze and remove toxic pesticide includes GC, HPLC or Column switching high-performance liquid chromatography (CSHPLC), GC/MS, HPLC/MS, Super-critical fluid extraction (SFE), capillary electrophoresis (CE), and enzyme linked immunosorbent assay (ELISA). Pesticide residue detection is often done using SFE [17]. In the past few years, electromigration methods like capillary electrophoresis, Capillary electro-chromatography (CEC) play a major role in identification and quality control of herbal drugs [22]. Some modifications in instrumentation helped in the revolution with better detection ability. In thin layer chromatography, the improvements include forced-flow planar chromatography (FFPC), rotation planar chromatography (RPC), over-pressured-layer chromatography (OPLC), and electroplanar chromatography (EPC) etc. Advances in HPLC includes HPLC analysis coupled with evaporative light scattering detection (ELSD), strong anion-exchange HPLC (SAX-HPLC), micellar electrokinetic capillary chromatography (MECC), high-speed counter-current chromatography (HSCCC), low-pressure size-exclusion chromatography (SEC), reversed-phase ion-pairing HPLC (RP-IPC-HPLC) etc [23]. Some technological aspects involved in herbal active principle and adulteration isolation, and detections have been tabulated in Table 3.

Table 3: Some technological aspects involved in isolation, and detections of active principle and adulteration in herbal medicine

Technology involved	Utilization	Reference
Chemical proteomics	Isolation and identification for binding partner of biologically active natural product	24
Use of DNA Barcode	Identification	25
Use of animal tissue culture models	For uptake And metabolism study of herbal drugs During digestion	26
DNA-based molecular markers like AFLP and RAPD Markers	Pharmacognostic characterization of herbal medicine	27
Chromatographic fingerprinting like High-performance thin-layer chromatography (HPTLC), High-performance liquid chromatography (HPLC), Ultra-high performance liquid chromatography (UPLC), Gas chromatography (GC) and multiple chromatographic profiling	Identification and isolation of herbal drug and adulterations	17, 28, 29
Hyphenated HPLC techniques, like with mass spectrometry (LC/MS), UV diode array (LC/UV) detection, nuclear magnetic resonance (LC/NMR), quadrupole time of flight (Q-TOF)	Identification of herbal drug and adulterations	28, 30
Capillary electrophoresis (CE) and other modified CE like Electrokinetic chromatography (EKC), Capillary zone electrophoresis (CZE)	Identification of herbal drug and adulterations	22, 28
Countercurrent chromatography (CCC)	Total recovery of sample, minimized tailing, less sample decomposition and solvent consumption during extraction	28
chemical fingerprinting combined with biological fingerprinting	Quality Control and prediction of severity	31

	of adverse reactions of herbal injections and to detect quality fluctuation	
Use of DNA micro-arrays	Gene expression studies by herbal drugs	32, 33
Biological Detection Technology like Immunoassay, sensor method	Detection and removal of pesticide residue from herbal medicine	17
Similarity search tool of chemiinformatics	To screen drugs for diseases	16, 31,34, 29,
Utilization of novel spectroscopic methods like FT-IR (Fourier transform infrared spectroscopy , near-infrared spectroscopy (NIR), Nuclear magnetic resonance (NMR) etc.	Identification purpose of herbal drugs	32

On the other hand, in herbal medicine research, DNA array also found its importance in efficacy testing. Effect of herbal extracts on gene expression is reported to be studied in cells and tissues [33]. Even genotoxicity assessment of the drug extract is also possible and carried out nowadays for toxicological potency assessment.

Multiple chromatographic profiling is one easy way considered for quality control of herbal drug. Classification and discrimination between herbal fingerprints and large data obtained thereafter are handled then by chemi-informatic tools like similarity search [29, 31, 34]. With the advancement of bio-informatics or chemi-informatics large databases of herbal medicine or secondary metabolites from various species have been set up which act as a substitute of various herbal pharmacopoeias. Bio-informatics-based identifications of plant secondary metabolites are possible through Madison Metabolomics Consortium Database (MMCD) whereas data about natural medicine can be obtained from Natural Medicines Comprehensive Database. HerbMed® is an interactive, electronic herbal database which provides information about herbs used for health and is maintained and updated by American Botanical Council. Some other database for natural product, herbal drug or alternative medicine includes NAPRALERT, Natural Medicines Comprehensive Database etc. Advancements in plant tissue culture techniques for more secondary metabolite production as well as modern techniques for isolation of medicinal compounds and pharmacological testing procedures are considered to be important issues today. Low cost bioreactors for plant tissue culture are being designed especially for commercialization of phytoconstituents[35]. Plant cell based bioprocessing is a new area of study of process optimization for maximum yield of plant derived compounds.

Adverse effects of herbal drugs: causes and types – To be minimized by technology

Pesticides have role in the regulation of plant growth and secondary metabolite production in cultivated medicinal plants, but residue levels have, so far, not been monitored. Nowadays various testing conditions are adapted to measure pesticide residue. They often cause adverse toxicities due to contamination [36]. The adverse effects also occur due to factors like adulteration, substitution, contamination and misidentification, lack of standardization, incorrect preparation and/or dosage, and inappropriate labeling and/or advertisement. Some toxic heavy metals like arsenic, lead, mercury, cadmium, [37] and undeclared drugs like Glibenclamide, mefenamic acid, etc. have been found in some Chinese as well as Indian traditional herbal product [38]. Now people are aware of these problems and various measures are being taken to solve the problems by forensic identification and by regulations. Not only it shows adverse effects, drug – drug and drug – excipient reactions are also considered important today. As many people is habituated in self herbal medication, it may cause adverse drug reaction with other prescription drugs and can complicate a situation as a study mentions that, commonly used herbal drugs like garlic, ginger, *Gingko biloba* are risk factors for intraoperative hemodynamic instability during pre or post operative period [39]. Considerable number of medicinal plants used in day to day life like Chinese herbal tea (used as health tonic) causes hepatic veno-occlusive disease (VOD) or Margosa oil from Azadirachta indica, a health tonic is also cause of Reye's syndrome [40]. Tea tree oil camomile causes contact dermatitis. Pharmacological interactions of herbal drugs with other medications were neglected previously but nowadays have also been taken into account. For example, *Gingko biloba* by interacting with aspirin and warfarin shows effects in coagulation of blood. Organ toxicity like neuropathy, nephropathy etc. due to contamination by pesticide residue, adulteration by other materials, misidentification are also major problems taken into account today which are being tried to be solved both by extensive research and increasing public awareness [41]. Cerebral arteritis, cerebral oedema, delirium, coma, confusion, encephalopathy, hallucinations, intracerebral haemorrhage and other types of cerebrovascular accidents, movement disorders, mood disturbances, muscle weakness, paresthesiae and seizures are some serious psychiatric and neurological adverse affects due to the effects of some herbal constituents [38]. Cases of neurotoxicity, hepatotoxicity, hematotoxity, nephrotoxity, cardiotoxicity have also been reported [42].

Formulation, dispensing and packaging

Stability studies related to herbal drug are considered important nowadays. Herbal drugs are generally dispensed in the form of pills, decoction, syrups, tablet, capsule etc. The physical instability of those herbal formulations or raw materials of herbal drugs are due to high moisture content, bacterial and fungal contamination, chemical instability, improper harvesting and storage condition etc. High moisture content also often facilitates bio-degradation of active constituents. These common causes of instability can be minimized by proper drying condition considering decomposition behavior of active constituents, nanoparticle coating of drug, use of chelating agent, formulation of emulsion and suspension etc [43]. Again, in most of the cases water soluble phyto constituents are the cause of limited bio-availability due to poor absorption in vivo. So, stabilization of the bio-active extract with a minimum shelf-life of over a year as well as techniques to increase bio-availability of phytochemicals are important areas of research. As biological activity of a herbal drug also depends upon drug delivery systems, various novel drug delivery systems like polymeric nanoparticles, nanocapsules, liposomes, phytosomes, nanoemulsions, microsphere, transferosomes, and ethosomes has been reported which in term help to increase the shelf life of the product and better and prolonged biological efficacy [44, 45]. For example curcumin liposome has been utilized as anticancer medication. Better biosorption was achieved with the discovery of herbosome. Herbosome consists of phosphatidylcholine which helps the phytoconstituent to enter the intestinal epithelial cell outer membrane which in term causes more bio-availability with better absorption properties [46]. Herbal excipients like starch, gums are also useful for manufacturing of herbal drugs with better bio-availability [47].

Other problems that should be of concern in herbal drug industry include lack of utilization of packaging technology for herbal drugs. Proper packaging is necessary so that it can be impervious to children and batch to batch product uniformity can be maintained. Proper labeling is also a part of packaging. In a recent paper it was stated that as no Good Manufacturing practice is maintained and concentration of active constituents are not indicated properly, which may cause toxicity when used for children [48]. Substandard processing, packaging or storage is great concerns for poor countries like Uganda [49]. Adopting newer techniques and implementing them, as well as focusing on search for new plants and natural materials containing plant products for medicinal purposes, the position of Chinese herbal market is rising while Indian herbal market is declining in global herbal market scenario [50, 51].

CONCLUSION

With the advancement of modern technology, people have paved up to a new era of herbal medicine. Still due to poor economic condition, many technologies are not possible to be implemented in developing countries for drug discovery, extraction, isolation and identification of important active principles or detection of toxic contaminants. So cheaper, easy to perform technologies for above mentioned processes are still being sought which would be needful for people of developing countries. Implementation of new small scale industrial collaboration utilizing indigenous plant sources for low cost herbal drug formulation production will be beneficial for primary health care system of third world countries. Though analysis of all other aspects discussed in this paper, it can be suggested that the era can be designated as herbal 'renaissance' due to rapid technological advancement of herbal medicinal industry and expansion of global herbal industry.

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