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# A REVIEW ON LATEST DEVELOPMENTS IN THE STANDARDIZATION OF AYURVEDIC DRUGS

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**Abstract:** Standardization of Ayurvedic formulations is an important step for the establishment of a consistent biological activity, a consistent chemical profile, or simply a quality assurance program for production and manufacturing of herbal drugs. WHO specific guidelines for the assessment of the safety, efficacy and quality of herbal medicines as a prerequisite for global harmonization are of utmost importance. An overview covering various techniques employed in extraction and characterization of herbal medicines as well as herbal Nano medicines standardization is reported. In addition, phytosomes increased bioavailability, bhasma as a metal Nano carrier drug delivery system, potential of metabolomics in the development of improved phytotherapeutic agents, DNA based molecular markers in distinguishing adulterants, and SCAR markers for authentication and discrimination of herbs from their adulterants are reported. Processed metals including Mercury, Gold, Silver, Lead, Zinc, Copper etc. were used very frequently by seers of the Indian tradition in different disease conditions with great authority. Recent advances in the study of minerals include petrological studies to analyze the physical and chemical changes in particular.

**Key Words:** Rasausadhi, Kastausadhi, Extraction technologies, Phytosomes, Nanocarrier drug delivery system, SCAR markers, DNA markers.

## *INTRODUCTION*

Ayurvedic compound formulations are broadly classified under the heading of Rasausadhi (predominantly metals and minerals are used for preparation and dealt in Rasashastra) and *Kastausadhi* (predominantly plant drugs are used for preparation and mainly dealt in Bhaisajyakalpana).

IN CASE OF RASAUSADHI: - It is generally claimed, that these are metals detoxified during the highly complex manufacturing process described in Ayurveda especially Rasashastra text. But still in an era of developing herbo metallic preparations proper validation and standardization is of utmost importance. Recent advances in the study of minerals include petro logical studies to analyze the structural changes in the samples before (raw), in process and after (finished) processing.

IN CASE OF KASTAUSADHI: - Herbal formulations have reached extensive acceptability as therapeutic agents for several diseases. The extraction of high-valued herbal compounds using microwave–assisted extraction and supercritical phase extraction technology followed by the standardization utilizing various spectroscopic, chromatographic and thermogravimetric techniques individually and/or in combination has been discussed in relation to herbal drugs. Capillary electrophoresis and polarographic techniques contributions towards standardization of herbal drugs is also reported. Nanotechnology based Chinese herbal drugs possess improved solubility and enhanced bioavailability.

In recent years, plant derived products are increasingly being sought out as medicinal products, nutraceuticals and cosmetics and are available in health food shops and pharmacies over the counter as self medication or also as drugs prescribed in the non-allopathic systems[1,2]. Standardization can be of two types[3] as follows:

**TRUE STANDARDIZATION: -** It represents a definite phytochemical or group of constituents known to have activity. Example- Gingko with its 26% Gingko flavones and 6% terpenes. These products are highly concentrated and no longer

represent the whole herb and now considered as phytopharmaceuticals.

**PSEUDO STANDARDIZATION:**

This is based on manufacturers guaranteeing the presence of a certain percentage of marker compounds; these are not indicators of therapeutic activity or quality of the herb.

During the medieval period, with the advent of Rasashastra, use of certain heavy metals and minerals in Ayurvedic therapeutics increased. Rasashastra, an integral part of Ayurveda, deals with the drugs of mineral origin, and details their varieties, characteristics, processing techniques, properties, therapeutic uses, possibilities of developing adverse effects and their management etc. in a comprehensive way. Ayurvedic classics like Charaka Samhita and Sushruta Samhita etc. contain descriptions of metals and minerals, their processing techniques and their utilization in therapeutics[4].

In case of, herbo mineral and metallic preparations occupied a significant seat in Ayurvedic pharmacopoeia and have routinely been used in practice in different parts of India for many centuries. Such preparations are held to be safe, efficacious even in minute doses, and, when manufactured and used following specified classical guidelines, not to lead to any significant untoward effects[5]. But to cope up with the demand of Ayurvedic medicines standardizations of such poly herbal formulations is a dire necessity.

Thus, in the broader sense standardization involves such unique techniques by which we can adjust the herbal drug preparation to a define content of a constituent or a group of substances with known therapeutic activity by adding excipients or by mixing herbal drugs.

**METHODOLOGY:-**

Methodology is divided in to following for the better indulgent:

1. Process standardization
2. Rasausadhis standardization
3. Overview on herbal drug standardization
4. Polyherbal standardization
5. DNA fingerprinting technique
6. Techniques in extraction of herbals
7. Phytosomes/ pharmacosomes: A novel drug delivery system for herbal drugs
8. Instrumental techniques for herbal drug standardization & identification
9. Herbal nanomedicines standardization

10. Global status of the regulatory guidelines for herbal medicines
11. Recent advancement in the methodology for the standardization of herbal medicines.

**Table 1**

Brief over view of the process of standardization

| Sr.No | Standardization of raw herbal drugs[3] | Norms to be followed during standardization[3] | Standardization of Herbal formulations[3,6]:- |
|---|---|---|---|
| **1** | Passport data of raw plant drugs | GSL(Good survey of literature) | Follow define GMP. |
| **2** | Correct taxonomic identification and authentication | GAP(Good agricultural practice) | Toxicity evaluation |
| **3** | Study on the medicinal part: root, stem, bark, etc. | GCP(Good clinical practice) | Chemical profiling |
| **4** | Collection details: location, stage and development, time storage etc. | GHP(Good harvesting /handling practice) | Pharmacodynamics |
| **5** | Organoleptic evaluation of raw drug | GLP(Good laboratory practice) | Pharmacokinetic |
| **6** | Microscopic and molecular examination | GMP(Good manufacturing practice) | Dosage |
| **7** | Chemical composition | GMT(Good marketing technique) | Stability |
| **8** | Biological activity of whole plant | - | Presentation and packing |
| **9** | Shelf life of raw drugs | - | Therapeutic merits |

**Table 2**

Standardization technique [6]

| Sr.No | Organoleptic | Botanical | Chemical | Biological | Physical |
|---|---|---|---|---|---|
| 1 | Colour | Macroscopic | Qualitative | Antagonistic | Moisture Content |
| 2 | Odour | Microscopic | Quantitative | Toxicological | Extractive Analysis |
| 3 | Taste | - | Chromatography | Pharmacological | Fluro Analysis |
| 4 | Texture | - | Heavy Metal | Others | - |
| 5 | Fracture | - | Pesticide Residue | - | - |
| 6 | Shape | - | Mycotoxins | - | - |
| 7 | External Marking | - | - | - | - |

**2. Standardization of Rasausadhis** (Herbo Mineral Formulations) [7]

Many herbo mineral formulations were developed for they were highly potent, quick in action, useful in many diseases and required in very minute quantities. Minerals and metals were taken from the mines with various impurities and toxins, so their use without purification was dreadful and toxic. Technologies those are available;

A. *Satvapatana* (Metal extraction) is a process adopted for the extraction of metals from their mineral of therapeutic importance.

B. *Puta* (Heating system) is a specialized method of providing heat to the material for converting them into bhasma form.

C. *Musa* (Crucible) is used for smelting and extraction of metal from the mineral.

D. *Kosthi* (furnace) is specially designed furnaces for providing heat during the process of satvapatana.

**Table 3**

Analytical techniques for Standardization of Rasausadhis

| Sr.No | Flame Test [8] (Flame Colour) | For Bhasma's (Medicated ash) | Mandura (Iron preparation) | Pisti (Powdered gemstone preparation) | Parpati (Metallic flakes preparation) |
|---|---|---|---|---|---|
| 1 | *Swarna* : Yellow | NOI[@] | NOI | NOI | NOI |
| 2 | *Rajat* : White | Description | Description | Description | Description |
| 3 | *Tamra* : Blue | Identification | Identification | Identification | Identification |
| 4 | *Vang* : Grey | LOD[#] at 110 $^0$c | Ash value | LOD at 110 $^0$c | LOD at 110 $^0$c |
| 5 | *Tuttha* : Red | LOI[$] | Assay of iron | Ash value | Assay (Hg, S) |
| 6 | *Bajra* : Multi | AIA* | - | Assay (Al, Ca) | - |
| 7 | *Shilajatu* : Ash like | Assay (Fe, As, Ag, Sn, Zn) | - | - | - |

@NOI-Name of Ingredients, #LOD-Loss on Drying, $ LOI-Loss on Ignition,*AIA-Acid Insoluble Ash

**Table 4**

History of important events in herbal drug standardization.

| YEAR | IMPORTANT EVENTS |
|---|---|
| 2007 | WHO. Guidelines for assessing quality of herbal medicines with reference to contaminants and residues. Geneva, Switzerland: World Health Organization; 2007. [9] |
| 2007 | WHO Guidelines on good manufacturing practices (GMP) for herbal medicines. Geneva, Switzerland: World Health Organization; 2007. [10] |
| 2009 | AYUSH department with collaboration with Quality Council of India ( introduced certification scheme for AYUSH drug products [11] |
| 2009 | USP. United States Pharmacopeia 32/National Formulary 27. Rockville, MD: The United States Pharmacopeial Convention; 2009. [12] |
| 2011 | An EU directive passed in 2004 erects "disproportionate" barriers against herbal remedies by requiring them to be "licensed" before they can be sold. It's called the Traditional Herbal Medicinal Products Directive (THMPD), Directive 2004/24/EC. [13] |
| 2011 | Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues." The document was published in the Federal Register on Tuesday, July 5, 2011. [14] |
| 2012 | National seminar on Recent Advances and Future Challenges in Ayurveda, Banaras Hindu University, Ganga kaveri publishing house, 2012. |

**4. Standardization of poly herbal formulation (multi-dimensional approach)**

Standardization is an important aspect for maintaining and assessing the quality and safety of the polyherbal formulation as these are combinations of more than one herb to attain the desire therapeutic effect[15]. The polyherbal formulation of hyperlipdemia has been standardized on the basis of

organoleptic properties, physical characteristics, and physico-chemical properties[16]. The formulation and standardized of a polyherbal formulation (Artrex®) designed for the treatment of arthritis containing four botanicals was carried out using modern scientific tools and with known markers, has been granted a US patent[17]. The standardization of various marketed herbal and polyherbal formulation [Madhumehari Churna (Baidynath) containing the mixture of eight herbal antidiabetic drugs *Momordica charantia* (seeds), *Syzigium cumini* (seeds), *Trigonella foenum* (seeds), *Azadirachta indica* (leaves), *Emblica officinalis* (fruits), *Curcuma longa* (rhizomes), *Gymnema sylvestre* (leaves), *Pterocarpus marsupium* (heart-wood)][18], Pancasama Churna known to be effective in gastrointestinal disorder[19], Dashamularishta, a traditional formulation, used in the normalization of physiological processes after child birth46, Gokshuradi Churna, Megni, Jawarish-e-Darchini[20] have been reported. But still there are many polyherbal formulations which require standardization as these are frequently used based only on their ethanobotanical use[21]. Standardization minimizes batch to batch variation; assure safety, efficacy, quality and acceptability of the polyherbal formulations[22]. Methiorep Premix (a combination of herbs viz. *Cicer arientinum, Phaseolus mungo, Mucuna pruriens, Triticum sativum, allium cepa* & richer source of protein with highly bioavailable methionine) has been recommended as a safe product to replace synthetic methionine in poultry ration and for supplementation in basal diet for regular usage[23]. TLC and HPTLC fingerprint profiles were used for deciding the identity, purity and strength of the polyherbal formulation and also for fixing standards for this Ayurvedic formulation[24].

**5. DNA fingerprinting technique**

DNA analysis has been proved as an important tool in herbal drug standardization. This technique is useful for the identification of phytochemically indistinguishable genuine drug from substituted or adulterated drug. It has been reported that DNA fingerprint genome remain the same irrespective of the plant part used while the phytochemical content will vary with the plant part used, physiology and environment[25]. The other useful application of DNA fingerprinting is the availability of intact genomic DNA specificity in commercial herbal drugs which helps in distinguishing adulterants even in processed samples[26]. Several studies have been done in past few years to

distinguish relation between DNA markers with phytochemical composition among closely related species[27]. Interspecies variation has been reported using random amplified polymorphic and random fragment length polymorphism DNA marker in different genera such as *Glycerrhiza*, *Echinacea*, *Curcuma* and Arabidopsis[27]. Proper integration of molecular techniques and analytical tools generated a comprehensive system of botanical characterization that can be applied in the industry level to ensure quality control of botanicals. DNA markers are helpful to identify cells, individuals or species as they can be used to produce normal, functioning proteins to replace defective ones. Moreover, these markers help in treatment of various diseases and helps in distinguishing the genuine herb from adulterated drug[28].

**6. Techniques in extraction of herbals**

A. Supercritical fluid extraction (SFE)

Supercritical fluid extraction (SFE) is the most preferable process for the extraction of the bioactive chemical from the medicinal and aromatic plants[29]. SFE has emerged as a highly promising technology for production of herbal medicines and nutraceuticals with high potency of active ingredients[30]. SFE techniques have been found useful in isolating the desired phytoconstituents from the herbal extracts[31].

B. Microwave-assisted extraction (MAE)

MAE technology includes the extraction of high-value compounds from natural sources including phytonutrients, nutraceutical and functional food ingredients and pharmaceutical actives from biomass[32]. MAE finds utility in production of cost effective herbal extracts and helpful in extraction of carotenoids from single cells, taxanes from taxus biomass, essential fatty acids from microalgae and oilseeds, phytosterols from medicinal plants, polyphenols from green tea, and essential oils from various sources. Compared to conventional solvent extraction methods, advantages of this technology include: a) improved product, purity of crude extracts, stability of marker compounds and use of minimal toxic solvents. b) reduced processing costs, increased recovery and purity of marker compounds, very fast extraction rates, reduced energy and solvent usage[33].

C. Solid phase extraction (SPE)

Methods, advantages of this technology include: a) improved product, purity of crude extracts, and stability of marker compounds and use of minimal toxic

solvents. b) reduced processing costs, increased recovery and purity of marker compounds, very fast extraction rates, reduced energy and solvent usage[33]. The solid-phase extraction was introduced for determining thirteen organochlorine pesticide residues including alpha-benzene hexachloride (BHC), betaBHC, gamma-BHC, delta-BHC, p,p'-dichloro-diphenyldichloroethylene (pp'-DDE), p,p'-dichloro-di-phenyldichloroethane (pp'-DDD), o,p'-dichloro-diphenyltrichloroethane (op'-DDT), pp'-DDT, heptachlor (HEPT), aldrin, heptachlor epoxide (HCE), dieldrin and endrin in *Scutellaria baicalensis, Salvia miltiorrhiza, Belamcanda chinensis, Paeoniae lactiflora, Angelica dahurica, Arisaema erubescens, Fructus arctii, Anemarrhena asphodeloides and Platycodon grandiflorum*. The organochlorine pesticides were extracted from herbs with mixed solvents of acetone and n-hexane by ultrasonic and cleaned up by Florisil solidphase extraction column[34]. Solid phase extraction was used to prepare the test solution for the analysis of aristolochic acid I and II in herbal medicines[35].

**7. Phytosomes/ pharmacosomes: A novel drug delivery system for herbal drugs**

Pharmacosomes commonly known as phytosome are drug-phospholipid complexes having active ingredients of the herb and can be formulated in the form of solution, suspension, emulsion, syrup, lotion, gel, cream, aqueous microdispersion, pill, capsule, powder, granules and chewable tablet[36]. Plants namely *Silybum Marianum*, *Ginkgo Biloba* and ginseng showed better efficacy than conventional herbal formulations[37]. In addition, the clinical trials of phytosomes have shown increased bioavailability in comparison to conventional herbal formulations generally containing polyphenols and flavonoids in humans[38]. Several phytosomal herbal drug delivery systems have been reported[39]. Researchers demonstrated increased bioavaliblity of four polyphenol phytosome preparations (curcumin, silybin, flavan-3-ol catechins and proanthocyanidin) and this effect was due to the intermolecular bonding between individual polyphenol molecules and one or more molecules of the phospholipid, phosphatidylcholine[40]. Phytosomal herbal drug delivery systems are mainly used i) to deliver systemic antioxidant (mainly polyphenols, flavonoid and terpenoid components), ii) useful in treatment of the disease like blood pressure,

liver disease, cancer, skin disease and iii) helps in protecting the brain lining.[40]

**8. Instrumental techniques used for herbal drug standardization & identification**

**A. High-performance liquid chromatography (HPLC)**

Preparative and analytical HPLC are widely used in pharmaceutical industry for isolating and purification of herbal compounds**.** There are basically two types of preparative HPLC: low pressure HPLC (typically under 5 bar) and high pressure HPLC (pressure >20 bar) [41].

The important parameters to be considered are resolution, sensitivity and fast analysis time in analytical HPLC whereas both the degree of solute purity as well as the amount of compound that can be produced per unit time i.e. throughput or recovery in preparative HPLC[42].

Vasicine, the major bioactive alkaloid of *Adhatoda vasica*, was estimated by HPLC in two polyherbal drug formulations - Shereeshadi Kashaya and Yastyadivati, and its content was found to be 18.1 mg/100 g in Shereeshadi Kashaya and 0.7 mg/100g in Yastyadivati[43]. HPLC analysis of Senna leaves provided informations about sennoside content, kaempferol 3-O-D-gentiobioside, aloeemodine 8-O-D-glucopyranoside, rhein 8-O-Dglucopyranoside, torachrysone 8-O-D glucopyranoside and isorhamnetine 3-O-D-gentiobioside L [44]. Standardization of the Triphala (an antioxidant-rich herbal formulation) mixture of *Emblica officinalis*, *Terminalia chebula* and *T. belerica* in equal proportions has been reported by the HPLC method by using the RP18 column with an acidic mobile phase[45]**.** The combination of HPLC and LC/MS is currently the most powerful technique for the quality control of Chinese herbal medicine Gan-Cao (licorice) [46].

**B. Liquid chromatography- mass spectroscopy (LCMS)**

LC-MS has become method of choice in many stages of drug development[47]. Chemical standardization of an aqueous extract of the mixture of the 20 herbs provided 20 chemical compounds serving as reference markers using LC-MS[48] Further, LC-MS analysis of amino glycosides showed that these drugs are highly soluble in water, exhibited low plasma protein binding, and were more than 90% excreted through the kidney. Further this technique helps in analysis of amino glycosides in

plasma samples with ion pairing chromatography[49].

Two HPLC methods, one combined with a photodiode array detector (LC/UV) and another with mass spectrometry (LC/MS), were reported for the analysis of aristolochic acid I and II in herbal medicines. The LC/ UV method was carried out using a Cosmosil 5C18-MS column with a gradient solvent system composed of phosphate buffer-acetonitrile and a UV detector (390 nm) while the LC/MS method was performed using an acetate buffer-acetonitrile solvent system and positive-ion electrospray ionization MS. The characteristic fragment ions for aristolochic acid I were selected at *m/z* 359, *m/z* 324, *m/z* 298, and *m/z* 296, and for aristolochic acid II at *m/z* 329, *m/z* 294, and *m/z* 26892.

**C. Supercritical fluid chromatography (SFC)**

SFC permits the separation and determination of a group of compounds that are not conveniently handled by either gas or liquid chromatography. SFC has been applied to a wide variety of materials including natural products, drugs, food and pesticide[50]. SFC enables the resolution of unknown components and known markers such as azadirachtin A and B, salannin, and nimbin in neem seed extracts[51].

**D. Capillary electrophoresis (CE)**

Researchers evaluated the importance of CE for quality control of herbal medicinal products[52]. Several CE studies dealing with herbal medicines have been reported and two kinds of medicinal compounds i.e. alkaloids[53] and flavonoids[53] have been studied extensively. The methodology of CE was established to evaluate one herb drug in terms of specificity, sensitivity and precision, and the results were in agreement with those obtained by the HPLC method. Furthermore, the analysis time of the CE method was two times shorter than that in HPLC and solvent consumption was more than 100-fold less[54]. A characteristic fingerprint of *Flos carthami* established using CE, simultaneously contributed to several objects in a study: identifying the raw herb, helping distinguish the substitute or adulterant and further assessing the differences of *Flos carthami* grown in various areas of China[55]. Comparison of the CE and HPLC fingerprints of *Radix scutellariae* showed a decrease in analysis time from 40 to 12min for CE, but also a decrease in detected peaks from14 to 11[56]. The hyphenated CE instruments, such as CE-diode array detection, CE-MS and CE-

NMR, have been utilized; however, some limitations of CE hyphenations with respect to reproducibility were reported.[57]

**E. Thermal analysis of herbal drugs**

Thermo gravimetric analysis (TGA), differential thermal analysis (DTA) and differential scanning calorimetry (DSC) have been employed to study any physical or chemical changes in various products including herbal drugs and also used to study pre formulation or drug excipient compatibility[58]. TGA may be operated under subambient conditions to analyse ethanol in herbal formulations such as asavas and arista[59]. TGA and DTA analysis of mercury based Indian traditional metallic herbal drug Ras-sindoor indicated the presence of mercury sulphide based on a sharp peak at 354o C which corresponded to melting temperature of mercury sulphide[60]. The optimized extraction obtained by distillation showed the presence of volatile oil in dry ginger as a component of volatile oil-beta-cyclodextrin inclusion compound using DTA[61]. DSC thermograms data confirmed the formation of phospholipids complex with emodin (an anthraquinone) [62] and naringen[63].

**F. Differential pulse polarography (DPP)**

DPP can be used to study trace amounts of chemicals with detection limits on the order of 10-8 M. Some heavy metals, including Pb, Cd, Zn, Cu and Fe were successfully identified and determined in chamomile and calendulea flowers by DPP[64]. Accumulation of heavy metals, namely Pb, Cd, Cu and Zn was estimated in market as well as genuine samples of important herbal drugs of India viz., *Alpinia galanga, Artemesia parviflora, Butea monosperrma, Coleus forskohlii, Curcuma amada, Euphorbia prostrate, Leucas aspera, Malaxis accuminata and Pueraria tuberose.* The concentration of Pb and Cd was found beyond the WHO permissible limits in most samples[65]. Trace a mounts of selenium in Chinese herbal medicines[66] and flavonoids in small amount of medicinal herb samples were determined by DPP[67]. A DPP method has been for the determination of total hypericin in phytotherapeutic preparations (drops, tablets and capsules) in various buffer systems over the pH range 3.5–10.0 [68].

**9. Standardization of herbal nanomedicines**

Herbal nanotechnology helps in incorporation of the active phytoconstituents to obtain desired therapeutic effect. The increased solubility, stability, bioavailability, pharmacological activity of

many popular herbal extracts including Milk thistle, *Ginkgo biloba*, grape seed, green tea, hawthorn, ginseng using nano dosage forms such as polymeric nanoparticles nanospheres & nanocapsules, liposomes, proliposomes, solid lipid nanoparticles, and nanoemulsion has been reported[69]. Other advantage of herbal nanomedicine include protection from toxicity, improving tissue macrophages distribution, sustained delivery, protection from physical and chemical degradation[69]. Silver nanoparticles of *Ocimum sanctum* extract exihibited maximum antibacterial activity at a dose of 150µg in wistar rats[70].The herbal drug incorporated antibacterial Nano fibrous mat fabricated by electrospin provided a potential application for use of wound dressing[70]. Nanotechnology patents issue in Chinese herbal medicine has been reported and proliferation of nanobased Chinese herbal medicine patents in China was due to the illusions of biomedical technology progress extensively[71].

**10. Global status of the regulatory guidelines for herbal medicines**

The US FDA has issued draft guidance for botanical products.[72] The regulatory approach is based on 1) intended use of botanical – as dietary supplement, cosmetic or drug and 2) status of botanical – marketed in US, marketed outside US or not marketed at all. The guideline is fairly exhaustive and pragmatic. The data requirements depend on several factors.

Some of the general guidelines are:

A. Traditional herbal medicines or currently marketed botanical products, because of their extensive though uncontrolled use in humans, may require less preclinical information to support initial clinical trials than would be expected for synthetic or highly purified drugs.

B. Requirements for Investigational New Drug (IND) applications of botanicals legally marketed in the United States as dietary supplements or cosmetics

Very little new chemistry manufacturing and controls (CMC) or toxicologic data are needed to initiate early clinical, if there are no known safety issues associated with the product and it is used at approximately the same doses as those currently or traditionally used or recommended. As the product is marketed and the dose thought to be appropriate and well tolerated is known, there should be little need for pilot or typical Phase 1 studies. Sponsors are allowed to initiate more definitive efficacy trials early in the development program. If there is

doubt about the best dose of the product tested, a randomized, parallel, dose-response study may be particularly useful as an initial trial.

C. Requirements for botanical product that has not been previously marketed in the United States or anywhere in the world.

Certain additional information (CMC, toxicology, human use) is required to assist FDA in determining the safety of the product for use in initial clinical studies. If the product is prepared, processed, and used according to methodologies for which there is prior human experience, sufficient information may be available to support such studies without standard preclinical testing.

D. Clinical trials of botanical products

There may be special problems associated with the incorporation of traditional methodologies, such as selection of doses and addition of new botanical ingredients based on response, which will need to be resolved. The credible design for clinical trials studies will be randomized, double blind, and placebo-controlled (or dose-response). For most conditions potentially treated by botanical drugs (generally mildly symptomatic), active control equivalence designs would not be credible. For expanded i.e., Phase 3 clinical studies on a botanical drug product, more detailed information on CMC and preclinical safety is necessary as compared to the information required for a Phase 1 or Phase 2 study. This additional information should be provided regardless of whether the product is currently lawfully marketed in the United States or elsewhere as a dietary supplement. All study data should conform to standard ethical guidelines of good clinical practice (informed consent, approval from ethics committee) for all clinical trials.

E. Documentation for early trials (IND)

Description of Product and Documentation of Human Use

- Description of Botanicals Used
- History of Use
- Current Investigational Use

Chemistry, Manufacturing, and Controls

- Botanical Raw Material
- Botanical Drug Substance
- Botanical Drug Product
- Placebo

- Labelling
- Environmental Assessment or Claim of Categorical

F. Exclusive marketing rights

US FDA has a provision to grant exclusive marketing rights for 3-5 years even in the absence of patent protection. During the period of exclusivity, FDA will not approve, or in some cases even review, certain competitor products unless the second sponsor conducts all studies necessary to demonstrate the safety and effectiveness of its product.

**11. Recent advancement in the methodology for the standardization of herbal medicines[73]**

Scientific evidence from randomized clinical trials is only strong for many uses of acupuncture, some herbal medicines and for some of the manual therapies. Only a small fraction of the thousands of medicinal plants used worldwide has been tested rigorously in randomized, controlled trials. Even if the animal studies or anecdotal clinical experiences are promising and use of an herb is widespread, such observations cannot predict the results of well designed randomized, controlled trials.A recent review concluded that evidence-based studies on the efficacy and safety of traditional Indian medicines are limited. The data available is mostly experimental or in animals. Most trials do not report hard efficacy endpoints and duration of observation periods is generally short. The clinical relevance of the observed effects is not always clear. For instance, most Indian trials of hepatoprotective agents are open and uncontrolled. As most acute liver conditions have a natural recovery, it is difficult to link the improvement to the herbal product. The essential ingredient in most formulations is not precisely defined. High quality studies are necessary to evaluate and compare the value of traditional Indian drugs to modern medicine. A fundamental problem in all clinical research of herbal medicines is whether different products, extracts, or even different lots of the same extract are comparable and equivalent. For example, Echinacea products can contain other plant extracts; use different plant species (E. purpurea, pallida or angustifolia), different parts (herb, root,

both), and might have been produced in quite different manners (hydro- or lipophilic extraction). Even different species may be known by the same name in local language. Brahmi refers to Centella asiatica and Bacopa monniera.

The herbal industry is not required to conduct clinical trials, and the industry professionals argue that it would be not be possible to recover the high research costs, as herbal products can not be patented as easily as new chemical entities. Nevertheless, randomized, controlled trials are the best way to demonstrate the efficacy of any medicine, herbal or conventional.

## *CONCLUSION*

Gone are the days when a vaidya used to collect, select, prepare and dispense medicines all by himself. Knowledge of Ayurveda is now being imparted through institution, colleges, hospitals and through ancient treatises. This has necessitated the establishment of standards for ayurvedic drugs and formulations so as to ensure proper use of the medicines so prepared for the benefit of the end user without any unwarranted complications. Thus standardization is needed to establish quality control parameters for each traditional drug before it is released for use without the fear of toxicity and contamination.

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