

Advancement of Standardization Process of Traditional Pharmaceuticals: A Review

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ABSTRACT

Around 75% - 80% of the world population is depending on traditional medicine and natural medicine for their primary health care needs. In the present era people looking towards traditional medicine for their health problems due to long term acceptability and also they believe that herbal medicine is safe and free from adverse effects. The development of quality control protocols for herbal medicines is an essential operation to ensure the safety and efficacy of herbal pharmaceuticals. The present review was focused to elaborate the evolution and advancement of application of quality concept and standardization of traditional pharmaceutical industry in past two decades. Peer reviewed articles and authentic texts were reviewed and compiled. Botanical parameters, physiochemical parameters, pharmacological parameters, toxicological parameters and chromatographic techniques had been introduced by WHO for Standardization of traditional pharmaceuticals. Macroscopic, microscopic, physiochemical, microbial quality, spectrophotometric had chromatographic techniques had been widely evolved to standardize herbal pharmaceuticals. At present, novel and advanced techniques had been popularized for standardization of herbal pharmaceuticals such as fluorescence quenching, combinations of spectrophotometric and chromatographic methods, DNA and chemical finger print methods. The results of this review revealed that the advancement of quality concept and standardization of traditional or herbal pharmaceuticals have been evolved with integration of continuously developed science based technologies.

Key Words- Traditional medicine, Quality control, Standardization

INTRODUCTION

Traditional medicine defines as collection of many therapeutic systems that have been continued for thousands of years and are still in use today [1]. Many of Traditional medical systems have been derived from ancient traditions of advanced civilizations. Traditional medicine is a unique medical system which has been passed down from generation to generation [2]. Some of the positive features of traditional medicine are diversity of treatment and medicine, flexibility, easy accessibility, relative low cost and low levels of technological applications [3].

Around 75% - 80% of the world population is depending on traditional medicine and natural medicine for their primary health care needs [4]. In present era people of developing countries and developed countries looking towards traditional medicine for their health problems due to long term acceptability and also they believe that herbal medicine is safety and free from adverse effects [5]. Ayurveda system of medicine as an ancient system of traditional medicine plays a significant role in field of traditional medicine [6].

According to Ayurveda, pharmaceuticals (*Aushadha*) are one of the

major requirements for the treatment to cure and prevent the diseases [7]. Therefore, different formulas, preparation methods of pharmaceuticals and therapeutic values of herbal, mineral materials have been described in authentic Ayurveda text. The discipline of preparation of Ayurveda pharmaceuticals is known as "*Bhaishajya Kalpana*"[8]. In ancient era the preparation of Ayurveda pharmaceuticals had been done by the physicians using traditional knowledge. These preparations were prepared to treat patients in domestic level [2].

They had been not practiced commercial level pharmaceutical preparation and also they were not much interested earning money for their treatments [9], but also interested on quality, safety and efficacy of pharmaceuticals. Availability of instruction and procedures for maintain the pharmacy in authentic text lead to prepare good quality pharmaceuticals in that era. Gardening of medicinal plants, well ventilated pharmacy building, free from disturbances by human being and any animals, consistent of the different types of instruments and equipment and consideration of Astrological opinion were the good practices in establishment of pharmacy [8,10]. They have been mentioned about qualities and characteristics of people those who have to be recruited to the pharmacy [8].

Over times, people's medical needs became more complex. The demand for herbal medicine is rapidly increasing both in the national market as well as internationally [3]. A tremendous pressure had been occurred on the pharmaceutical process chain and domestic level pharmaceutical manufacturing process was not sufficient to meet the demand of herbal pharmaceuticals [11]. Therefore, assistant workers had been joined for pharmaceutical preparation process and also had to buy the raw materials from the market. Then, gradually commercial herbal pharmaceutical industry has been evolved.

Herbal powdered preparations, internal or external pastes, extractions, tinctures, pills, decoctions, syrups, medicated wines and oils have been introduced to the market and people prone to purchase these traditional pharmaceutical items with or without medical prescriptions. Extraction, fraction, purification, incineration, concentration or other physical or biological processes and traditional method of pharmaceutical preparations have been used for pharmaceutical preparations [12].

Gradually, numbers of commercial manufacturing units have been evolved in the society, especially in India and Sri Lanka [11]. Considering the development of industry many regulatory authorities have been established in world wide. While expanding the industry modern quality concept and standardization of herbal medicines were raised in the society with consideration of quality, safety and efficacy of commercial products and also the World Health organization was emphasized the requirement of quality herbal products by using modern quality control techniques and applying suitable standards. According to Shinde et al., 2009 quality control and standardization of traditional pharmaceuticals is an essential operation processes in the traditional or herbal pharmaceutical industry [12]. In 1975, WHO regulated a set of legal guidelines under Good Manufacturing Practices (GMP) and issued various quality standards guidelines for evaluating the quality of raw materials, preparation process as well as finished herbal pharmaceutical products [8,13]. Whatever the organization or regulations, aim of them is to ensure safety and efficacy of herbal pharmaceutical products [8]. Correct botanical evaluation and identification of medicinal plants, establishing standardization parameters, quality control process in raw material and product processing, assessments of stability of finished products are the key factors of standardization and quality controlling process [12,14].

Testing of finished products to ensure quality, safety and efficacy of products prior to release to the market is a result of these guidelines [15]. In 2008 according to Yadav and Dixit revealed that authenticity, purity and assay are the major attributes, which are desirable for standardization and quality assurance of herbal pharmaceuticals [14].

With this background this review was focused to elaborate the evolution and advancement of application of quality concept and standardization of traditional pharmaceutical industry in past two decades. Peer-reviewed articles and authentic texts were reviewed and compiled.

Advancement of quality concept and standardization

The application of Good Agricultural and Collection Practice (GACP), Good Agricultural Practice (GAP) in medicinal plant cultivation and processing for herbal pharmaceutical products plays an important role in quality concept and also serve to protect medicinal plants for sustainable usage [16]. GACP have been recommended as a standard test procedure for assessing the identity, purity and content of medicinal plant materials [17]. GAP guidelines cover the area of seed selection, growth conditions, use of fertilizers, harvesting, drying and storage [16]. WHO gives standard guidelines to develop of national pharmacopoeia and monographs of medicinal plants, as well as Standard techniques for cultivation and conservation of medicinal plants [12]. Standardizations protocol as botanical parameters, physiochemical parameters, pharmacological parameters, toxicological parameters and chromatographic techniques had introduced by WHO [18].

Also many of criteria were developed to prove identity and purity of medicinal plants and herbal pharmaceuticals. Macro- and microscopic identification, sensory property evaluation, physical constants, adulteration and contaminants have been introduced as

botanical parameters. The macroscopic characteristics are useful for identification process and its include the shape, size, color, texture, fracture aspects and characteristics of the external appearance and cut surfaces. The microscopic characteristic details are obtained from a microscopic view, with or without the addition of chemical reagents and it is helped to ensure the identification [19].

The botanical verification of the crude material is prime importance in establishing the quality of herbal pharmaceuticals. Qualitative chemical examination carried out using different analytical techniques has been proposed to identification, verification, purification and characterization of active constituents of raw materials in terms of standardization process of herbal Pharmaceuticals [16]. This process has been contributed to develop new standard phyto-medicine since last two decades.

Loss of drying, moisture, total ash content, alcohol and water soluble extractive values have been introduced as physiochemical parameters and these parameters have been documented as standard parameters for herbal pharmaceutical in several pharmacopeias worldwide. Bitterness value, hemolytic Property, astringent property, swelling index and foaming index are also have been introduced as Pharmacological standard parameters in WHO standardizations protocol [18].

Later the focus shifted towards test of purity of herbal materials. These test are being used to evaluate different types of contaminations happening in herbal materials during the growing, harvesting, transporting, storing and processing. Biological contaminations such as pests, insects, microbes, pesticides and heavy metals. Further to this special protocol has been developed as toxicological parameters, microbiological standards, permissible level of heavy metals and permissible level of radioactive compounds [20]. While gradually developing parameters for standards, the

advanced analytical techniques such as photometric analysis, thin layer chromatography (TLC), high performance thin layer chromatography (HPTLC), liquid chromatography (LC) high performance liquid chromatography (HPLC), and gas chromatography (GC) had been integrated with standardization process of traditional herbal pharmaceuticals [21]. Later on hyphenated standard analytical techniques like liquid chromatography coupled with mass spectrometry (LC-MS), gas chromatography-mass spectroscopy (GC-MS) and liquid chromatography- nuclear magnetic resonance (LC-NMR) have been widely used to ensure the quality and safety of herbal pharmaceuticals [22].

Some recent advanced techniques such as capillary electrophoresis [21], supercritical fluid chromatography (SFC), Micellar Electro-Kinetic Capillary Chromatography (MECC), High-Speed Counter-Current Chromatography (HSCCC), low-pressure Size-Exclusion Chromatography (SEC), Reversed-Phase Ion-Pairing HPLC (RP-IPC-HPLC), and Strong Anion-Exchange HPLC (SAX-HPLC) have been used to separate specific compounds from herbal resource for modern phyto-medicinal development [23].

Thermo gravimetric analysis (TGA), differential scanning calorimetry (DSC) and differential thermal analysis (DTA) are some thermal techniques using for qualitative and quantitative drug analysis process [23]. Chemo - metrics, Polarography, Differential Scanning Calorimeter (DSC), Molecular biomarkers in fingerprints (DNA fingerprint) are recently employed in standardization of herbal drugs [18]. One of the latest methods for the classification of herbal pharmaceuticals are Linear Discriminant Analysis (LDA), K-nearest neighbors (k-NN), Artificial Neural Networks (ANN), Soft Independent Modelling of Class Analogy (SIMCA), Partial Least Squares-Discriminant Analysis (PLS-DA) and Latent Structures-Discriminant are the techniques that could be used in future to manufacture better

quality, safety and efficacious herbal pharmaceuticals [19].

Some significant developments in quality control methods for herbal medicines have been introduced in last few years. New descriptions of markers as quality control tools and the methods of determination, application on qualitatively and quantitatively determination of chemical profiles for the certain herbs in herbal medicines, determination of sample detection limit and its verification and novel statistical techniques of validation methods are some of new techniques has been introduced to pharmaceutical industry as quality control tools [13].

DISCUSSION

Considering the global requirements of standardization of herbal pharmaceuticals use of evolved techniques has been used and documented in last two decades.

In 2019, Deogade and Prasad have been done a study to standardize the Kushnatulasi (*Ocimum tenuiflorum* Linn/*Ocimum sanctum* L) collected from wild. In this study authentication and standardization have evaluated by morphological or organoleptic tests, microscopic, chemical, and physical evaluation, chromatography, spectrophotometry [24].

In 2014 Kokare et al., had been reviewed and proposed the necessity of developing standardization parameters for herbal fine powder. In the study they were emphasized the need of physical, chemical, biological and analytical parameters to assure the quality, safety and purity of herbal medicine [25]. Traditional Indian herbal powder named Pancasama *Churna* had been standardized by using macro-microscopic, Physico-chemical, preliminary phytochemical, TLC and HPTLC methods [26].

A poly-herbal Iranian traditional herbal syrup had been reformulated and standardized with various physiochemical tests and pharmaceutical parameters, including macroscopic characteristics, crystallization evaluation, cap locking,

sedimentation, dried residue, pH, density, microbial evaluations, viscosity measurement, evaluation of rheological properties, accelerated stability tests and short term thermal stability [27]. In 2011, Gharate and Kasture had been conducted standardization study for a selected herbal wine. pH value, Acid value, Level of alcohol, Microbial load, Pesticide residues, Heavy metals contents were used as parameters to standardization of medicated wine [28]. Many of other studies had been focused on assessing the microbial quality and standardization of few herbal liquid oral preparations available in the Indian market [29-31].

The hyphenated HPLC techniques has been widely used for the analysis of the bioactive chemical compounds in plants and herbal medicines [21]. In 2008 Alwakeel had been conducted the study to evaluate microbial contaminants and presence of toxic heavy metals in some herbal pharmaceuticals. Microbial count evaluation tests and Atomic Absorption Spectrophotometry (AAS) were applied for the study [32].

Microbiological quality of 20 herbal products as tablet, powder and capsule (solid dosage forms) had been examined in Iran for quality assurance of herbal pharmaceuticals available in the market [33].

The pharmaceutical and microbial qualities of 21 dosages form of different traditional medicine had been investigated in south western Nigeria. Table/capsule properties, powder properties, solutions properties, class of compounds and microbial content of samples were determined and proved the requirement for constant monitoring and control of the standards of herbal medicines form the study [34]. In 2014, Zhou et al., had been analyzed the compound profiles of famous traditional Chinese medicinal formula with UHPLC-Q-TOF/MS method (ultra-high-performance liquid chromatogram coupled with electrospray ionization tandem quadrupole-time of flight/mass spectroscopy) [35]. In 2006 Zeng et al., have

been investigated the chemical composition (phenolic components) of *Salvia miltiorrhizae* by high-performance liquid chromatography/electrospray ionization tandem mass spectrometry (HPLC/ESI-MS/MS) [36]. The phytochemical analysis of Traditional Chinese Medicine had been conducted by Yang et al., using High-Performance Liquid Chromatography coupled with Mass Spectrometry (HPLC-MS) in 2009 [37]. In 2006, Tang et al., had been developed a study based on capillary electrophoresis method for separation and determination of epicatechin, isovanillic acid, vanillic acid and myricetin in *Dioscorea bulbifera* L. and its medicinal preparations [38].

In 2014, advanced techniques on chromatographic fingerprinting in standardization process on determination the concentrations of a set of characteristic chemical substances in *Andrographis paniculata* had been reviewed by Rajalakshmi et al [39]. DNA fingerprinting technique and chemical fingerprint technique of herbal pharmaceuticals can be mentioned as a complement tool of other quality control techniques [19]. DNA fingerprint technique had been identified as an advanced technique useful for the identification of genuine drug from substituted or adulterated drug [40]. In 2015, Lekha et. al. reviewed about "Chemometrics" which is one of the recent techniques for authentication and identification of the medicinal herbs by using chemical integrities [41]. In 2017, Alam and Mishra reviewed that the need of ensure the quality of the herbal pharmaceuticals using modern analytical techniques, for therapeutic efficacy and safety [42]. Nowadays, Chromatographic and spectroscopic fingerprint analysis, including TLC, HPLC, GC, CE, IR, NMR, as well as DNA fingerprinting techniques, are widely applied for quality assurance of traditional medicine. As well as advanced hyphenated technologies such as GC-MS, HPLC-MS, and LCNMR are used to obtain well accurate and much more information about

analysis, quality control and metabolite studies of traditional medicine. Supercritical Fluid Chromatography (SFC) is a new eco-friendly technology which can be used for purification of herbal constituents. SFC is mainly focused to identify the fractions of pollutants like polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), pesticides, dioxins or open-chain hydrocarbons from herbals as well as herbal pharmaceuticals [43]. In 2016 Sajeeb et al., had been introduced simple, precise and cost effective RP-HPLC method for quality control and standardization of traditional and herbal medicines [44]. They attempted to standardize the market preparations of *Adathoda vasica* via quantitation of its major metabolite by RP-HPLC method. Wang et al., had been mentioned Conventional Electrospray Ionization Mass Spectrometry (ESI-MS) method is used for analysis of solution samples [45]. In 2014 they had been developed pipette-tip ESI-MS, a technique that combines pipette tips with syringe and syringe pump, for direct analysis of herbal powders. Attenuated Total Reflection – Fourier Transform Infrared Spectroscopy (ATR-FT-IR) method has been widely used in Chinese herbal pharmaceutical industry, as quality control tool for direct identification and quantitative estimation of herbs or extracts. Different grades of *Panax notoginseng* powders were differentiated by using FT-IR and 2D FT-IR and combination of ATR-FTIR micro-spectroscopy methods were applied directly for identification the complex mixtures of herbal powders [13]. Due to the causes of industrialization, fertilizer, agricultural pesticides, pollutants, storage, and marketing process natural origin of medicinal resources expose and contaminate with many of ionic and non-ionic elements. ICP-MS (inductively coupled plasma-mass spectroscopy) and PIXE (partial induced X-ray emission) are the common methods which have been used for analytical and chemo-metric studies as safety profiles on herbs [23].

CONCLUSION

The results of this review revealed that the advancement of quality concept and standardization of traditional or herbal pharmaceutical have been evolved with integration of continuously developed science based technologies and highlighted advanced features of evolution of herbal pharmaceutical industry for better world.

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- How to cite this article: Udahapuvida BMMSHK, Weerasooriya WMB, Liyanage JA. Advancement of standardization process of traditional pharmaceuticals: a review. *Int J Health Sci Res*. 2020; 10(12):294-301.
