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DRUG STANDARDIZATION AND ITS APPLICATIONS TO HERBAL/SKIN CARE FORMULATIONS: A REVIEW

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Abstract
The rising interest in herbal and natural therapies for health care restoration, beauty enhancement, and disease prevention has led to the renewed demand for nutraceuticals. While the pharmaceutical industry is now moving towards phyto-pharmaceuticals to meet this increasing demand to have assurance of the quality, safety and effectiveness of herbal medicines. In this respect drug standardization has become an important process ensuring that herbal drugs satisfy the pharmacopoeial standards of identity, purity, potency and contamination control. This reviews studies highlighting the significance of standardization of drug in herbal and skin care product and focuses on the techniques, methods available in nature to prepare standardized available preparations. These include chemical, microscopic and spectrometric analyses, as well as more sophisticated techniques like chromatography, electrophoresis or DNA fingerprinting. The paper further discusses the role of pharmacopoeial reference materials established by WHO and other international organizations and the difficulties in detecting active agents responsible for medicinal properties. With the rising concerns regarding the side effects of modern drugs, herbal medicines including skin care products need to be standardized for their efficacy and safety. This will include the importance of Good Manufacturing Practices (GMP) and quality control in ensuring consistency and avoiding contamination or misidentification. Finally, drugs standardization is the future of herbal products to guarantee their acceptance and effectiveness in current medicine and protection from the risks related to their consumption.

1. Introduction
People in old age use natural medicines as home remedies to cure different diseases, to enhance their beauty, reduce ageing and as natural nutrients. Even now a days, attraction towards natural therapies is increasing as the concept for safe and effective medicines is gaining popularity, people are moving towards the herbal products for their primary health care needs. The concept that the herbal medicines have fewer side effects, easily available and are cost effective, has led the pharmaceutical industry towards the use of phyto-pharmaceuticals and the demand of the herbal products is increasing day by day. At the end of eighteenth century and with the start of nineteenth century demand for herbal remedies reached its peak but suffered a major decline at the start of twentieth century due to the isolation and production of structurally similar compound. Around fifty years later herbal medicines gained popularity again due to an increase in the number of side effects from modern medicines. One of the popular uses of herbal material is their incorporation in skin care creams for whitening, moisturizing and fairness. For this purpose many herbal materials are

added to the creams for their beneficial actions. These contain sweet almond, olive, peanut, corn, wheat, bees wax, wheat germ, jojoba, lecithin, vitamin E oil and many others (Fursenco et al., 2023).

Drug Standardization refers to a system that involves the processes to ensure identity, safety, purity, efficacy, quality and quantity of the ingredient in each dose (Bele and Khale, 2011; Chaudhury, 1992; Choudhary and Sekhon, 2011; Ekka et al. 2008; Kunle et al., 2012; Yadav and Dixit, 2008; Zafar et al., 2005). Standardization also deals with the herbal medicines and includes such methods and techniques by which herbal medicines can be prepared with improved quality and potency and with reduced side effects.

The medicinal use of herbs is known from the beginning of history of human civilization. In recent years, there has been a growing interest in herbal medicines among healthcare professionals, scientists and general public (Blumenthal, 1999a,b; Blumenthal et al., 1998; Calixto, 2000; Gautam et al., 2010; Hussain et al., 2009; Jia and Zhang, 2005; Roberts and Tyler, 1998; Vadiya and Devasagayam, 2007; Zhang et al., 2012). Herbal medicines are the ones that contain plant materials or a part of plant as an active ingredient along with other excipients (Bulletin of WHO, 1993; Bulletin WHO, 1998; Kosalec et al., 2009; Ritch, 2000). In the case of plant material, either crude or processed, usually, the main compound responsible for the therapeutic activity is not known. A fact known for the phyto-pharmaceuticals is that they do not show immediate therapeutic effect, therefore, they are not used in emergency cases mostly. The usually described three classes of herbal medicines include: herbal materials either crude or modified, traditionally used products and the phyto-pharmaceuticals that are finished standardized herbal formulations (Iwu et al., 1999).

Side effects of herbal medicines with impurities like ephedra causing cardiovascular problems, asthma medicines causing reduced visceral activity, licorice causing water retention and hypertension, senna causing hepatitis, lily causing cardiac shock and many others gave rise to the concept of drug standardization and impurity detection (Cuzzolin et al., 2006; Elvin-Lewis, 2001; Sahoo et al., 2010).

The increase in the use of herbal medicines is due to increased incidence of adverse effects resulting from the use of modern medicines. The greater use of herbal medicines requires their standardization, and clinical trials for maintaining the quality and efficacy of a product. In order to ensure the quality of herbal preparations validated analytical methods must be used for standardization (Kushwaha et al., 2010; Ong, 2004; Wani, 2007). Traditionally, the products containing herbal material were used for nutrition, cosmetics and for different ailments but now they are also being used as phyto-pharmaceuticals for certain diseases.

For the standardization of herbal drugs the implementation of Good Manufacturing Practice (GMP) is essential. Standardization tests and methods are available in Indian Herbal Pharmacopoeia (2010), British Herbal Pharmacopoeia (1996), Japanese Standards for Herbal Pharmacopoeia, (1996) and in the Quality Control Methods for Medicinal Plant Materials (WHO, 1996) and are also stated in other pharmacopoeias.

Two types of standardization can be carried out these includes true standardization which guarantees the presence of compounds in herbs in definite proportions having therapeutic activity and pseudo-standardization that deals with the percentage of marker compound present in the plant material, these markers are not indicators of pharmacological activity of a drug (Bose et al., 2012; Hussain et al., 2009; Jones and Chin, 2006). However, in certain cases biomarker compounds are also used that indicates the pharmacological activity of the drug.

2. STANDARDIZATION TESTS AND METHODS

WHO has proposed guidelines for herbal products to help their members and other countries in ensuring the safety and efficacy of herbal drugs (Petrovick et al., 1999; Ziesel, 1999). According to the pharmacopoeias, for the standardization and quality control of herbal medicines, different parameters are used for testing which include chemical identification, microscopic and macroscopic evaluation, purity, assay and contamination testing of various drugs (Bhutani, 2003; Kokate et al.,

2004). Along with these tests, different biopharmaceutical parameters related to the dosage form are also performed and checked for reproducible results (Ong, 2004).

Macroscopic evaluation includes identifying parameters like taste, odor, color, size, shape and texture, whereas, the microscopic evaluation involves identification and the comparison of different entities in herbal material (Patel et al., 2006). Advances in microscopy specially scanning electron microscopy (SEM) and light scattering electron microscopy (LSEM) has increased the accuracy in the identification of herbal crude materials (Mosihuzzaman and Chuodhary, 2008).

For the evaluation of the identity, purity and assay, different analytical methods can be used. In addition to microscopic and macroscopic evaluation, generally, physical methods are also used for determining the identity and constituents in plant materials or in herbal medicines. These methods include the determination of moisture content, melting point, refractive index, optical rotation, viscosity, etc. whereas chemical methods are used to determine acid value, acetyl and ester value, iodine value, etc.

Purity and identity can be determined by spectrometric analysis which includes Ultra-Violet and visible spectrometry, Infrared spectrometry, Mass spectrometry, and NMR spectroscopy. Chromatographic methods include thin layer chromatography (TLC), high performance thin layer chromatography (HPTLC), high performance liquid chromatography (HPLC), gas liquid chromatography (GLC) are also used to confirm purity and identity of herbal constituents (Ahirwal et al., 2006; Gupta and Sharma, 2007).

Assay is perhaps the most difficult task to perform on phyto-pharmaceuticals as in most cases the compound responsible for therapeutic activity is not known. For this purpose mostly the analytical methods stated above are used while in some cases combination of these methods like HPLC-MS, LC-MS, LC-NMR, GC-MS are used. Other methods include capillary electrophoresis, supercritical fluid chromatography, ultra-performance liquid chromatography, DNA finger printing and polarography (Rajani and Kanaki, 2008).

Currently chromatography, spectrometry, electrophoresis, polarography and the use of finger print technique are employed for the determination of biomarkers in the standardization process. Herbal drugs contain several chemical constituents in a specific ratio which can be used as biomarkers for qualitative as well as quantitative determination.

Drugs should be free from microorganisms, radioactive compounds, pesticide residues, heavy metals, adulterants, foreign matters and contaminants like insects, moulds, fecal matters, etc. (Ernst, 2002; Ernst, 2001; Mazzanti et al., 2008; Rai et al., 2001). In order to maintain the quality of herbal medicines WHO and other organizations have set the limit of pesticide residues along with heavy metals (European Medicine Agency, 2006; The Pharmacopoeia Commission of China, 2005).

3 HERBAL/NON-HERBAL PHARMACOPOEIAL REQUIREMENTS FOR QUALITY CONTROL AND STANDARDIZATION

The acceptance of herbal medicines by general public has led the pharmaceutical industry towards the use of phyto-therapeutic agent. About 80% of the world population prefers herbal medicines for different ailments as they consider herbal medicines safe, cost effective and free from side effects. Maintenance of the quality of herbal products is very crucial and it involves all the stages from the start of cultivation of plant to the clinical trials including post surveillance studies. For this purpose World Health Organization (WHO) has given guidelines on Good Agricultural and Collection Practices for Medicinal Plants. For herbal drug standardization and quality control, WHO has also given guidelines which include parameters like identity, physicochemical characteristics, pharmacological and toxicity studies, microbial and radioactive studies (Shrikumer et al., 2006).

For the quality management of phyto-pharmaceuticals the criteria of quality shall be set for individual herbs that should include complete specification in the form of a monograph like those found in the pharmacopoeias. The regulation of the quality and safety of herbal drugs were recommended to the drug control agency by WHO (1996). Furthermore, for the standardization of mono-herbal drugs a detailed protocol was given by World Health Organization (Pattanayak et al., 2011).

In addition to the pharmacopoeias, the monographs on standardization of different plant materials can be found in WHO monographs for medicinal plants (WHO monographs on Selected Medicinal Plants, 1999, 2002, 2007, 2009), Herbal Medicine expanded Commission monograph (Blumenthal, 1998), and British Herbal Compendium (Bradley, 2010), The therapeutic and pharmacological activity of herbal materials can be cited in different books (Evans, 2002).

4 INDUSTRIAL IMPORTANCE OF STANDARDIZATION IN MAINTAINING QUALITY AND EFFICACY OF HERBAL PRODUCTS

Increase in the demand of herbal products has highlighted the value of herbal industry. With increase in the development of herbal drugs, needs to standardize these products for potency of their active ingredient and efficacy to ensure their quality has also increased. The quality control of crude drugs and herbal formulations is very important to justify their acceptance and use in modern system of medicine. Standardization of herbal medicine is the first step in maintaining the quality and efficacy. It is estimated that about 25% of the modern medicines have originated from plant materials either directly or indirectly (Cragg et al., 1997; De-Smet, 1995, 1997; Duke et al., 2002; Shu, 1998). In the under developed countries along with developed countries like Unites States, Germany, France and Italy with traditional use of medicinal plants, it is mandatory to standardize all the herbal medicines and to ascertain their efficacy as is done in the case of synthetic medicines (Brevoort, 1995, 1995; Fisher and Ward, 1994).

Drug standardization plays an important role in maintaining the quality and efficacy of a drug as a medicine should be safe and effective whether obtained naturally or synthetically. Standardization of a drug minimizes batch to batch variation, eliminates contamination and increases the therapeutic effect and shelf life of a drug (Ahmad et al., 2006).

Numerous phyto-pharmaceuticals are used internationally for various ailments and include morphine, digitoxin, diosgenin, atropine, colchicine, quinine, reserpine, vincristine, podophyllin, castor oil, anthraquinones, atrimisinine, taxol and several antibiotics. Therefore, in order to maintain the quality and efficacy of a drug, standardization is very essential. Research following the clinical trials has shown, the idea that the herbal medicines are safe and free from side effects, is false (Razmovski-Naumovski et al., 2010).

Herbal medicines have been reported for two types of side effects, that is, intrinsic factors which are related to the herbal medicines themselves including the cases of allergic reactions, over dosing etc., whereas, the second factor is extrinsic which is related to the manufacturing problems, mishandling, misidentification, lacking of cGMP and standardization, adulteration, incorrect preparation, etc. (Bagheri et al., 1998; Brinker, 1998).

In Pakistan Hamdard Laboratories (Waqf) Pakistan, Qarshi Industries (Pvt.) Ltd and Ajmal Laboratories are the leading industries in the manufacturing of herbal products. Research on standardization, quality control and safety of herbal products is done at HEJ Research Institute of Chemistry, University of Karachi, Hamdard University, Karachi, National Institute of Health, Islamabad and in many other universities (Hussain et al., 2009).

5. SOURCE OF INFORMATION ON DRUG STANDARDIZATION

Pharmacopoeias

Herbal Pharmacopoeias

British Herbal Pharmacopoeia (1996), Indian Herbal Pharmacopoeia (2010), American Herbal Pharmacopoeia (2016), Korean Herbal Pharmacopoeia (2019), Thai Herbal Pharmacopoeia (2020), Pharmacopoeia of the People's Republic of China (2020).

Non-Herbal Pharmacopoeias containing monographs on herbal drugs

U.S Pharmacopoeia (2021), British Pharmacopoeia (2022), Chinese Pharmacopoeia (2020), Japanese Pharmacopoeia (2021), European Pharmacopoeia (2021), Indian Pharmacopoeia (2022).

Books
Dubey (2014), Waghulkar (2011), Zafar et al. (2010), Shamkuwar (2013)

Chapters in Books
Bandaranayake (2006), Kamboj (2012), Rajani and Kanaki (2008), Barbosa (2012).

World Health Organization Guidelines
Quality control methods for herbal materials (2011), General guidelines for methodologies on research and evaluation of traditional medicines (2000, 2001, 2005), Guidelines on good agricultural and collection practices (2003, 2004), Supplementary guidelines on good manufacturing practices for the manufacture of herbal medicines (2006), Research guidelines for evaluating the safety and efficacy of herbal medicines (1993), guidelines for assessing quality of herbal medicine (2007).

Reviews
Chaudhary et al. (2021), Gautam et al. (2010), Mosihuzzaman and Choudhary (2008), Nikam et al. (2012), Ong (2004), Thirumalai (2011), Sahil et al. (2011), Garg et al. (2012).

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