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CURRENT REGULATORY PERSPECTIVE OF HERBAL DRUGS

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Abstract:

The current challenging aspect of herbal medicine or traditional system is maintenance of quality, safety and efficacy issues. As there is a global recognition for the herbal drugs as an healing aids, the demand for these traditional system have been increased drastically from 19th century to 21st century. As the main challenge of this herbal medicine / drugs is maintenance of DNA finger printing, phytochemical and therapeutic uniformity, lack of Good clinical practices, standard operating protocols, no proper protocols or guidelines on pharmacokinetic and pharmacodynamic issues , no standardisation protocols, no control on residual limits (Pesticide residues, Microbe residues, heavy metal residues, solvent residues and teratogenicity). In order to meet this challenges the regulatory agencies EMEA, ICH AYUSH, WHO, USFDA trying to bring these herbal therapies/drugs under regulatory pipeline under the NDA approval process. In order to meet these current challenges, the Indian Herbal Pharmacopoeia *has published 40* monographs *monitored by* Indian *Drugs Manufacturers Association (IDMA). The current review focuses on the current trends in herbal drug safety monitoring and regulatory aspects of Herbal therapeutics.*

Keywords: Herbal medicines, Therapeutic uniformity, Standardisation, Regulatory challenges.

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1.INTRODUCTION

1.1. Demand for Herbal Medicine

The demand for herbal medicine has been drastically increased from 19th to 21st century when modern system of medicine failed to address challenging diseases like cancer, psoriasis, tuberculosis, osteoarthritis etc. Till today we are highly depend on the natural sources for discovery of new drug leads in treating these diseases and this traditional medicine (TM) has been ignored by this modern society and there was high chances of adulteration (Yuan et al., 2016) .

It was in the end of 20th century and start of 21st century, the importance of traditional drugs and traditional medicine was recognised globally and made to think of the quality, safety, efficacy issues of these drugs (Fabricant & Farnsworth., 2001, Fung et al., 2015).

1.2. Current challenges in Herbal drugs

With increase in demand of herbal drugs, there are many challenges need to be addressed by modern regulation specialists. The challenges are lack of content uniformity, lack of official monograph for every traditional drug, stability issues, residual ratios like heavy metal, pesticides, radioactive contaminants, aflatoxins etc. The serious continuing challenge is usage of herbal medicine, their safety issues in sense of complete pharmacokinetic and pharmacodynamic profiles, herb- drug interactions, adverse effects, no solid record of clinical trials, no correct or adequate information to clinicians, pharmacovigilance and also patients about multiple healing properties to promise safety and efficacy towards consumer (Elena et al., 2016).

Even though natural products became sole sources for new drugs due to diversity of different functional primary and secondary metabolites of plants, phytoalexins, fungus, algal and mineral sources. Traditional methods failed in identification and characterisation of these new molecules. In order to validate the identification, quantification, structures and biological properties of such phytoconstituents there is an urgent need for development of new high throughput analytical bioinformatic tools like proteomics, metabolomics and 3D printing techniques (Ngo et al., 2013).

Another big challenge for herbal drugs is their authentication of originality, this can be countered by developing a new hybrid high through put techniques like DNA finger printing and bar-coding information for their genetical identity. Even though a great attempt was made by regulatory authorities, it was a still a big challenge in 21st century as many plants don't have DNA finger printing and bar-coding information. It was a mandate authentication process in most of the developed countries before starting a research from plant sources.

In this current decade, this DNA fingerprint concept is in high demand for determination of genetic history of plants and its genotypic characterisation in order to find the strict genus and species nature.

Eg : species variation of *Phyllanthus amaraus and Phyllanthus niruri* and also to differentiate between various substitution varieties of Ocimum ,Embelia, Solanum and Zingiber species (Selva Kumar et al., 2017).

1.3. Foreign organic matter (FOM)

The Foreign organic matter is a common contaminant in the herbal drugs. As per WHO, any matter or residue that is present apart from labelled description of monograph can be consider as foreign organic matter.

The FOM may also be a moulds or insects, including excreta and visible contaminant such as sand or silicaceous matter, poisonous harmful foreign matter, chemical residues and animal matters such as insects and microbes, which can produce toxins, are also among the potential contaminants of herbal medicines (WHO, 2004, 2003; EMEA, 2002).

FOM should be regulated in market within limit as per WHO guidelines. Even though many death issues happening due to foreign contaminants, there are no

scientific evidences or documentation in form of literature or publications. Hence this became difficult for the authors to represent the clinical data in this article.

1.4. Phytochemical complexity of Phyto-pharmaceuticals

Plant consist diversity in its phytoconstituents, it is quite difficult to have a clear total phytochemical data that is responsible for targeted biological activity. It is mandate to know clear total phytochemical fingerprint nature of each plant. Even in 21st century after having modern tools like chromatography and spectroscopy, the modern sciences failed to document total phytochemical finger print and complex interactions between phytochemicals. Still the concept of multitargeting effect of phototherapeutics is unclear (Efferth & Koch, 2011).

Even incidents like discovery of hyperforin proved that hypericin is less potent and stable than hyperforin, till 19th to 20th century, Science assume that hypericin is only the phytochemical marker responsible for various therapeutics and it was changed after discovery of hyperforin (Vollmer & Rosenson, 2004). Even for the regulatory agencies it has become a big issue to regulate and document the phytochemical complexity reactions.

1.5 The complex pharmacokinetic interactions & adverse effects

Another example for this issue is having bottle guard (*Lagenaria siceraria*) juice as a herbal drug as its traditional claims saying that it is good antidiabetic and antihyperlipidemic. But few cases were reported that due to unknown complex interaction of terpenoid bitters with other molecules in the juice can lead to death due to intestinal bleeding and no antidote is available in this poisoning due to complexity.

It is a duty of regulatory bodies to educate the public about interactions of herbs with other drugs, foods and other herbs as well to safeguard quality, safety and efficacy issues (Ankur & Sanjay., 2015).

The challenge in herbal based medicine is lack of full crystal clear clinical pharmacokinetic documentation that includes adverse effects and interactions. Most of these herbalpathy can be consider as polytherapy and complication is drug-drug interaction and complete documentation is again challenging until live incident happens (Palleria, Caterina et al., 2013).

1.6. The Residual Analysis

Residual analysis is another challenge in herbal drugs or supplements. Residues of solvent, microbials, heavy metals, pesticides, photoxics, aflatoxins, teratogens, siloxanes and polymers impart dangerous health impact. Residual analysis has no attention till 21st century till realising their bio accumulating hazardous health effect. WHO has specified limits for these residues? (Marco et al., 2010). Most of these residues have teratogenicity and phototoxicity and hence the residual analysis should be mandatory by regulatory authorities.

1.7. Toxicity Issues

Despite of many health benefits against mild to life threatening disease, many negative toxicity issues have been documented due to lack of quality control on herbal medicines or dosage forms. Adverse effects of the herbals are mainly manifested as discomfort, vomiting, allergic reaction etc. There are several herbs with narcotic derivatives as their constituent that may cause dependency or damage CNS (Mohi et al., 2018).

Many herbs are having potential toxic constituents which cause severe damage to vital organs like or carcinogenic. it is found that most of the herbal aphrodisiacs and antihyperlipidemic are responsible for hepatotoxicity eg: Ephedra, Kava (Haller et al., 2000, Teschke et al., 2010).

Toxic effects of Aconite, Datura seeds, Aloevera juice Areca seeds already been reported in many literatures. (Philomena et al., 2011). Allergic reactions to chamomile tea is well discussed by andres and co-workers in their article. (Andres et al., 2009).

Ginseng is liable to produce abuse, manifestation syndrome involves diarrhea, hypertension, insomnia, nervousness and skin eruption. (**Doo Jin Paik and Chang Ho Lee, Review of cases of patient risk associated with ginseng abuse and misuse. J Ginseng Res. 2015 Apr; 39(2): 89–93.)** Often herbal formulations are admixed with synthetic adulterants like sildenafil, alprazolam, warfarin and many steroids. The Adverse effects in herbal drugs need to be monitored, otherwise they will end up with serious ill effects may lead to death of individual.

1.8. Clinical Issues

The main lacuna in regulation of herbal medicine globally is lack of documentation on clinical issues on herbal medicines. Due to many life hacking clinical interactions and adverse effects happened due to non-regulated use of herbal drugs, it is urgent global regulatory requirement mandate for health care providers for documenting new herb interactions in order to monitor the safety and efficacy issues. It is also mandate to document medication history of

patients where they are using herbal drugs (Firenzuoli et al., 2007).

1.9. The concept of NDA in herbal drugs

Even the Global regulatory authority (CDSCO) considers phytopharmaceuticals as NDA only. This main motto of this new regulation is to promote herbal drug as a trustful entity having quality, safety and efficacy information and it will help to accept herbal products by modern sciences as healing entity. As per this new regulation policy it is must to have chemistry manufacturing control (CMC data), preclinical data and clinical data including safety and toxicity. As per this new regulation, documentation of good practices like GAP (Good Agriculture Practices) , GHP (Good harvesting practices), GCP (Good collection practices), GSP (Good storage practices), GDP (Good distribution practices), GMP (Good manufacturing practices) & GCP (Good clinical practices (Bhat., 2016).

1.10 Herbal Monographs

A monograph is defined as a specialised skilful art where the entire important information is gathered under one place. There are many herbal monographs like Ayurvedic monograph, Siddha Mongraph, Unani monograph, American herbal monograph, British herbal monograph, WHO Monograph, the monographs are an essential tool to regulate the quality, safety and efficacy of herbal drugs (WHO Monograph., 1999).

1.11. Finger printing Analysis

The Finger print analysis is very important regulatory concept that need to be mandated regulatory policy in herbal drugs inorder to safe guard the quality and safety issues. The DNA finger printing is an essential quality parameter in preventing the adulteration and identifying right genetic quality. The main problem is lack of chemical uniformity and inorder to assess this content uniformity, the phytochemical finger print and marker analysis by using HPTLC, HPLC and LCMS is very needful (Songlin et al., 2008).

1.12. National Policy on Traditional Medicine and Regulation of Herbal Medicines - Report of a WHO Global Survey

From the last decade, there is a high demand in the use of Traditional, Complementary and alternative medicine (TCAM) in both developed and developing countries and these therapies have been playing an important role in global health care. Hence the quality, safety, efficacy have become an important concern for both regulation authorities and society.

There are many challenges in regulation of herbal medicine in assessing quality, safety and efficacy but there is no information or documentation on these data especially on traditional healing concept and this may lead to many death cases due to may be of toxic adulterant, contamination or due to clinical adverse effects. In order to meet these challenges regulatory agencies like WHO, Ayush are coming out of many guidelines for safety assessing of herbal drugs. even updating of monographs is a part of this national policy (National policy on traditional medicine., 2005).

2. CONCLUSION:

As globally, there is a high demand and trust towards herbal therapies and it is must to have regulatory policies in order to meet the challenges like content uniformity, stability, bio similarity, clinical toxicity issues. Hence this review is explaining the need on the modern perspectives in regulating quality, safety and efficacy of herbal medicine.

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