Review Article

Challenges and Prospective Solutions in Non-classical Herbal Formulations: A Review

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Non-classical herbal formulations have gained momentum in the recent past. These formulations, however, have not been well integrated with the modern system of medicine in most of the countries in the world. This is due to the lack of enough scientific evidence pertaining to its long-term safety and efficacy. Besides, the paucity of authentic monographs on the impurity profiling, standardization protocols, lack of guideline on the fixed-dose combinations and absence of programmed pharmacovigilance plan for herbal drugs are among the major caveats. In recent years, few issues pertaining to the classical herbal formulations are being addressed to some extent. However, the issues on non-classical modern formulations remain the same. Hence, the objective of this mini-review is to shed light on the major flaws and challenges of these formulations and provide some expert opinion to counter these issues.

Key words: Non-classical herbal formulations, challenges, standardization

Drugs from natural sources have been used by most of the world population since time immemorial for the prophylaxis and treatment of various dreaded ailments. Modern medicine despite substantial development has failed to cater to the needs of people from diverse socio-economical class[1]. Hence, the majority of the population from the weaker section of the society, residing in a rural area largely depends on herbal medicine. Moreover, these traditional medicines have also become popular among a larger world population due to its lesser side effects and cost. The herbal medicine market is expected to grow at a compound annual growth rate of ~7.2 % during 2017-2023 and is predicted to reach $ 111 billion by the end of 2023[2]. Despite escalating growth, these medications are not the primary choice of treatment to date. However, these are used as adjunctive therapy along with primary treatment in many developed countries. This is due to the lack of integration of traditional medicine with the modern treatment, lack of explicit regulatory framework[3] and quality standards. In addition to this, the most profound caveats of traditional medicine are lack of established official standardization techniques and evidence-based safety and efficacy data[4]. Even in the new WHO traditional medicine strategy 2014-2023, the paucity of research data is one among the topmost challenges faced by the majority of member states[5]. Hence, the objective of this review is to shed light on the persistent challenges encountered in standardizing these herbal preparations, emphasizing more on non-classical proprietary herbal formulations.

Challenges in the standardization of non-classical proprietary herbal formulations:

Classical herbal formulations are those which are prepared according to the formula given in the traditional books of alternative systems of medicines like *Charaka Samhita*, *Sushruta Samhita*, *Bhaishajya ratnavali* and *Shanghan Lun* (classical Chinese medical treatise). The manufacturers of the classical herbal formulations follow the same formula to prepare the formulations and standardize as per the guideline of official monographs. On the contrary, non-classical or proprietary formulations are prepared as per manufacturers own formula and many a time the ingredients and additives are not found in the traditional literature. Most of the proprietary herbal

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preparations consist of a complex heterogeneous mixture. Though some of the materials are included in different official monographs, their chemical markers and chromatographic specifications are not well documented[6]. The analytical limits for the active constituents present in the modern herbal formulation cannot be so precise like pure chemicals. This is due to the inherent inconsistency of the active constituents present in the raw materials due to variation in the age and origin of the medicinal plant, method of cultivation and processing[7]. Hence, standardization of these products should include monitoring of the raw material right from its origin until its clinical application. Besides the challenges in herbal drug standardization has been discussed in detail by Chawla *et al*.[4], hence, this review emphasizes more on the standardization of non-classical proprietary herbal formulations. Majority of these formulations composed of a varied number of components. Table 1 shows the composition of 4 established brands of herbal cough formulations available in the Indian market. Few ingredients in all the 4 formulations are common, but their strengths vary. There is no specific guideline on the strength of the components to be used in these formulations. Though sporadically the safety and efficacy of these formulations are studied[8,9], the patient population and study design is not enough to establish the long-term safety and efficacy of these preparations. Standardization of these formulations requires a state-of-the-art research facility with high end modern analytical instruments. For this activity, either the manufactures should have their own in-house center or can depend on the government approved testing laboratories. Majority of the small and medium

TABLE 1: COMPOSITION OF SOME PROPRIETARY HERBAL COUGH REMEDIES

Formulation1 constituents	Each 5 ml contains	Formulation2 constituents	Each 5 ml contains	Formulation3 constituents	Each 5 ml contains	Formulation 4 constituents	Each 5 ml contains
Ocimum tenuiflorum	50 mg	Mel despumatum	1.25 g	*Adhatoda vasica*	200 mg	*Anacyclus pyrethrum* Rt.,	10 mg
Glycyrrhiza glabra	50 mg	*Balsamodendron mukul*	35 mg	*Solanum xanthocarpum*	200 mg	*Cubea officicinalis* Fr.,	10 mg
Viola odorata	50 mg	*Vitis vinifera*	35 mg	*Piper chaba*	10 mg	*Piper nigrum* Fr.	10 mg
Solanum virginianum	50mg	*Ocimum sanctum*	25 mg	*Pistacia integerrima*	10 mg	*Zingiber officinale* Rz.	10 mg
Abies webbiana	50 mg	*Hyssopus officinalis*	25 mg	*Fagonia arabica*	10 mg	*Curcuma longa*	20 mg
Zingiber officinale	25 mg	*Tinospora cordifolia*	20 mg	*Clerodendron serratum*	10 mg	*Piper longum*	30 mg
Curcuma longa	25 mg	*Adhatoda vasica*	15 mg	*Pluchea lanceolata*	10 mg	*Clerodendron serratum*	40 mg
Justicia adhatoda	25 mg	*Myristica fragrans*	15 mg	*Curcuma zedoaria*	10 mg	*Viola odorata*	50 mg
Curcuma zedoaria	25 mg	*Glycyrrhiza glabra*	15 mg	*Plumbago zeylanica*	10 mg	*Juniperus communis*	50 mg
Mentha piperita	3 mg	*Onosma bracteatum*	10 mg	*Cyperus rotundus*	10 mg	*Ocimum sanctum*	60 mg
Shudha Madhu	1.75 g	*Viola odorata*	10 mg	*Zingiber officinale*	10 mg	*Terminalia bellirica*	100 mg
Flavoured syrup base	*q.s.*	*Triphala*	9 mg	*Piper nigrum*	10 mg	*Solanum xanthocarpum*	120 mg
-	-	*Trikatu*	9 mg	*Piper longum*	10 mg	*Glycyrrhiza glabra*	150 mg
-	-	*Embelia Ribes*	6 mg	*Glycyrrhiza glabra*	10 mg	*Adatoda vasica*	200 mg
-	-	*Solanum xanthocarpum*	8 mg	-	-	*Navsar*	15 mg
-	-	*Cinnamomum cassia*	3 mg	-	-	Sodium benzoate	15 mg
-	-	*Nausadar*	3 mg	-	-	Sodium methyl paraben	8 mg
-	-	-	-	-	-	Sodium propyl paraben	1 mg
-	-	-	-	-	-	Sugar	2550 mg
-	-	-	-	-	-	Liquid glucose	1800 mg
-	-	-	-	-	-	Citric acid monohydrate	q.s
-	-	-	-	-	-	flavour grape 1400	17.5 mg
-	-	-	-	-	-	Purified water	q.s

scale manufacturers of herbal drugs have financial constraints to have their own in-house testing facility. The limited number of governments approved testing laboratories for herbal drugs is a major hurdle for chemical characterization and biological evaluation of the proprietary formulations.

In India, along with the indigenous Ayurvedic system of medicine other alternative systems of medicine like Siddha and Unani are in practice since a prehistoric period. Although there is a similarity between the basic principle of treatment in these three systems of medicine, there are differences in formulations and method of standardization. The modern Ayurvedic formulations include tablets, capsules, syrups, solutions. Similarly, most of the Siddha formulations utilize mineral and metal in the formulations. These formulations are categorized into *Uppu*, *Pashanam*, *Uparasam*, *Ratnas* and *Uparatnas*, *Loham*, *Gandhakam*. Siddha system of medicine also includes drugs of animal and plant origin having a similar profile as that of Ayurvedic drugs. However, standards pertaining to the limit of impurities, heavy metals, and toxins in modern Siddha formulations are not defined in the Siddha Pharmacopeia of India. Hence, the standardization of Siddha formulations becomes a challenge. Due to the proximity of a few Siddha drugs with Ayurvedic preparations, the earlier can be standardized in a similar fashion as that of the later preparations. Unani system of medicine got introduced into India during 1350 AD. Since then this system of medicine has undergone many folds of development and modernization. The Government of India, Ministry of AYUSH has developed the Unani Pharmacopeia of India. This official monograph constitutes 50 classical Unani formulations and their standardization techniques, and limits of heavy metal content are also mentioned. However, the modern aspects of good manufacturing practice for herbal drugs were not addressed sufficiently in the published monographs.

Beside active ingredients, several excipients are used in modern herbal formulations to enhance the palatability, bio-absorption, and shelf-life of the formulations. These excipients vary based on the type of formulations. Solid dosage forms require diluents, binder or adhesives, lubricants, glidants, disintegrants, superdisintegrants, coloring agents, sweeteners, coating material, plasticizers. Similarly, liquid and semiliquid preparations require solvents, co-solvents, buffers, antimicrobial preservatives, thickening agents, wetting agents, humectants, emulsifying agents, sweetening agents, emollients, flavors. These excipients are basically of synthetic and natural origin. The non-classical modern herbal formulations contain both types of excipients. In many cases, lack of compatibility studies pertaining to additives leads to instability of the formulations. Hence, compatibility study of the additives in the formulation needs to be performed to ensure product quality.

Non-classical herbal formulations (modified herbal preparations) represent the modification of the indigenous classical herbal preparations either by changing dosage form or route of administration or method of preparation or using for different indications. Hence, these modified preparations most likely get impaired due to incompatibility, instability and impurity leading to serious adverse events due to toxicity. More than 16 000 suspected case report of adverse effects of herbal medicinal preparations have been reported in the WHO database till date. The most frequently reported adverse effects are face edema, hepatitis, hypertension, angioedema, convulsions, dermatitis, and death. The committee for proprietary medicinal products prepared a list of 33 drugs having serious risk factors and it was published by the European Commission in the year 1992. The WHO has come forward with a set of quality control standards for the modern herbal preparations. The safety and efficacy of herbal drugs are dependent on the extent of quality control. Hence the quality of the herbal drugs must be ensured right from the cultivation till preparation of the finished product. The WHO has published quality control methods for medicinal plant materials as a guide for quality control of botanicals. With reference to contaminants and residues WHO has developed a new guideline for assessing the quality of herbal medicines[10]. In Japan, where herbal drugs called *Kampo* medicine undergo stringent regulatory framework as that of the allopathic system of medicine and are well integrated. The manufacturer of a new herbal product needs to submit details of heavy metal content, aflatoxin details, mycotoxin, and pesticide details to the regulatory authority. Along with these documents the manufacturer needs to submit chemistry, manufacture and control (CMC) documents prior to market authorization. However, in the US submission of CMC document is not mandatory for herbal drugs manufacturers at investigational new drug stage. It becomes a herculean task to standardize the herbal formulation due to the presence of multiple components in a modern formulation. In Germany,

phytoequivalence, a newer concept was developed to ensure the consistency of the herbal formulations[11].

MODERN APPROACHES IN THE STANDARDIZATION OF PROPRIETARY HERBAL FORMULATIONS

Chemical methods of characterization are more acceptable for standardization of herbal formulations in the modern era. Some of the modern approaches and associated challenges are discussed below.

Chromatographic fingerprinting technique:

Since a long time, chromatographic fingerprinting techniques were used for identification of the single chemical entity. However, in recent years, these techniques have shown a new avenue in the phytopharmaceutical research. The techniques like thin-layer chromatography, high performance liquid chromatography, high-performance thin-layer chromatography, gas chromatography and liquid chromatography-mass spectrometry are broadly used for the identification of genuine crude drugs; active chemical components and their stability in proprietary herbal formulations. In case of the presence of a known constituent, it should be quantitated. On the contrary, a marker compound is used to standardize the drug when the active phytoconstituents are not known. To ensure the content uniformity of phytoconstituents across batches in a polyherbal formulation, single or multiple marker compounds are used. Numerous studies reported the use of chromatographic fingerprinting as a potential tool for standardizing complex polyherbal formulations[12-15]. The chromatographic fingerprinting for standardization of herbal formulations is an approved modern analytical technique by the USFDA and the WHO[16,17]. However, these techniques have some caveats, for example, nearly similar fingerprints do not always represent the same chemical constituent in the samples. This is because the chemical constituents in the preparation might have altered due to instability and diverse sources of crude drugs[18]. Hence, the simultaneous estimation of multiple components should be performed to estimate the chemical pattern of the components present in the formulation.

Impurities:

Impurities get into the herbal formulations at various stages of preparation[19] including deliberate adulteration of the herbal formulations with synthetic drugs[20,21]. The other sources of impurities include heavy metals, aflatoxins, pesticides and solvent residues in which the plant material is being extracted or fractionated. Limits of these impurities are prescribed in different official monographs presented in Tables 2 and 3[22-31]. However, complete information pertaining to the limit of residual solvents in individual plant extracts are lacking in most of the official monographs. Impurities produced in the herbal formulation due to degradation should be closely monitored. Few attempts were made in the recent past to perform the stability studies of the herbal formulations[32,33]. However, comprehensive guideline needs to be formulated exclusively for stability study of the herbal preparations.

Limits for microbial count:

Presence of microorganisms in natural products is an inherent phenomenon. Hence, there should be guideline prescribing the limit of aerobic microorganisms in the herbal products. Till date, there is no substantial monograph, which defines the percent and extent of acceptable total yeast count, molds and other harmful bacteria in an individual plant or animal extract.

As per the discussion, most of the modern non-classical herbal formulations are prepared according to the manufacturer's own formula. Many a time these formulations contain impurities due to known or unknown adulterants. There is a lack of stringent guideline and monographs for the control of these adulterants in these formulations. Safety and long-term efficacy studies are among the pivotal concerns in evaluating the potency of these formulations. Checking the authenticity of the source material from which the drug is being extracted, purity of the extract and chemical assay of the finished formulation can control the quality of the preparations to a major extent. Lack of sophisticated testing facility of herbal drugs is also a major concern which needs to be addressed by the government agencies in underdeveloped and developing countries. Lack of chemical marker for individual components present in the formulation is a critical challenge encountered by a manufacturer. Hence, a few governments led policies for the easy availability of diverse marker compounds seems to open a wider avenue for standardization of these modern herbal preparations. There is a need to establish a fixed dose combination for non-classical herbal preparations to control the quality and uniformity of the formulations. More exhaustive monographs pertaining to the content of microbial and aflatoxin limits in individual herbal components need to be

developed for reference. Fig. 1 explains the challenges associated with non-classical herbal formulations and their prospective solutions. In most of the countries, herbal drugs are regarded as an alternative system of medicine and are not well integrated with the modern system of medicine. Hence, the regulations pertaining to the quality of these formulations are not stringent. Many a case, these preparations are used among the populations by word of mouth and dispensed without a prescription from a qualified physician. Hence the use

TABLE 2: LIMITS OF HEAVY METALS AND AFLATOXINS[22-31]

HM/Afla	IP	JP	EP	USP	AP	UP
Lead	NMT 20 ppm	NMT 20 ppm	5 ppm	NMT 5 ppm	NMT 10 ppm	10 ppm
Mercury	-	-	0.1 ppm	NMT 20 ppm	NMT 1 ppm	1 ppm
Bismuth	-	-	-	NMT 20 ppm	-	
Arsenic	NMT 10 ppm	-	-	NMT 3 ppm	NMT 3 ppm	3 ppm
Antimony	-	-	-	NMT 20 ppm	-	
Tin	-	-	-	NMT 20 ppm	-	
Cadmium	-	-	0.5 ppm	NMT 20 ppm	NMT 0.3 ppm	0.3 ppm
Silver	-	-	-	NMT 20 ppm	-	-
Copper	-	-	-	NMT 20 ppm	-	
Molybdenum	-	-	-	NMT 20 ppm	-	
Vanadium	-	-	-	-	-	
Palladium	-	-	-	-	-	
Platinum	-	-	-	-	-	
Gold	-	-	-	-	-	
Ruthenium	-	-	-	-	-	
Afla B_1	-	10 µg/kg		NMT 5 ppb	0.5 ppm	
Afla G_1	-	10 µg/kg		NMT 20 ppb	0.5 ppm	
Afla B_2	-	10 µg/kg		NMT 20 ppb	0.1 ppm	
Afla G_2	-	10 µg/kg		NMT 20 ppb	0.1 ppm	

HM- Heavy metal, Afla- aflatoxin, IP- Indian Pharmacopoeia, JP- Japanese Pharmacopoeia, EP- European Pharmacopoeia, USP-United states Pharmacopoeia, AP- the Ayurvedic Pharmacopoeia of India, UP- the Unani Pharmacopoeia of India, NMT- not more than, Ppm-parts per million and ppb- parts per billion

TABLE 3: LIMITS OF RESIDUAL SOLVENTS

Class-I toxic and carcinogenic		Class-II less toxicity		Class-III low risk to human health	
Solvent	limit (ppm)	Solvent	limit (ppm)	Solvent	limit (ppm)
Benzene	2	Acetonitrile	410	Acetic acid	5000 ppm
Carbon tetra chloride	4	Chloroform	60	Acetone	5000 ppm
1,2-dichloroethane	5	Cyclohexane	3880	1-Butanol	5000 ppm
1,1-dichloroethane	8	Hexane	290	Anisole	5000 ppm
1,1,1-trichloroethane	1500	Methanol	3000	2-Butanol	5000 ppm
-	-	Nitromethane	50	Dimethyl sulfoxide	5000 ppm
-	-	Pyridine	200	Ethanol	5000 ppm
-	-	Tetra hydro furan	720	Ethyl acetate	5000 ppm
-	-	Toluene	890	Ethyl ether	5000 ppm
-	-	Xylene	2170	Ethyl formate	5000 ppm
-	-	-	-	Formic acid	5000 ppm
-	-	-	-	Heptane	5000 ppm
-	-	-	-	Isobutyl acetate	5000 ppm
-	-	-	-	Isopropyl acetate	5000 ppm
-	-	-	-	Methyl acetate	5000 ppm
-	-	-	-	Pentane	5000 ppm
-	-	-	-	1-Pentanol	5000 ppm
-	-	-	-	1-Propanol	5000 ppm

Ppm- parts per million

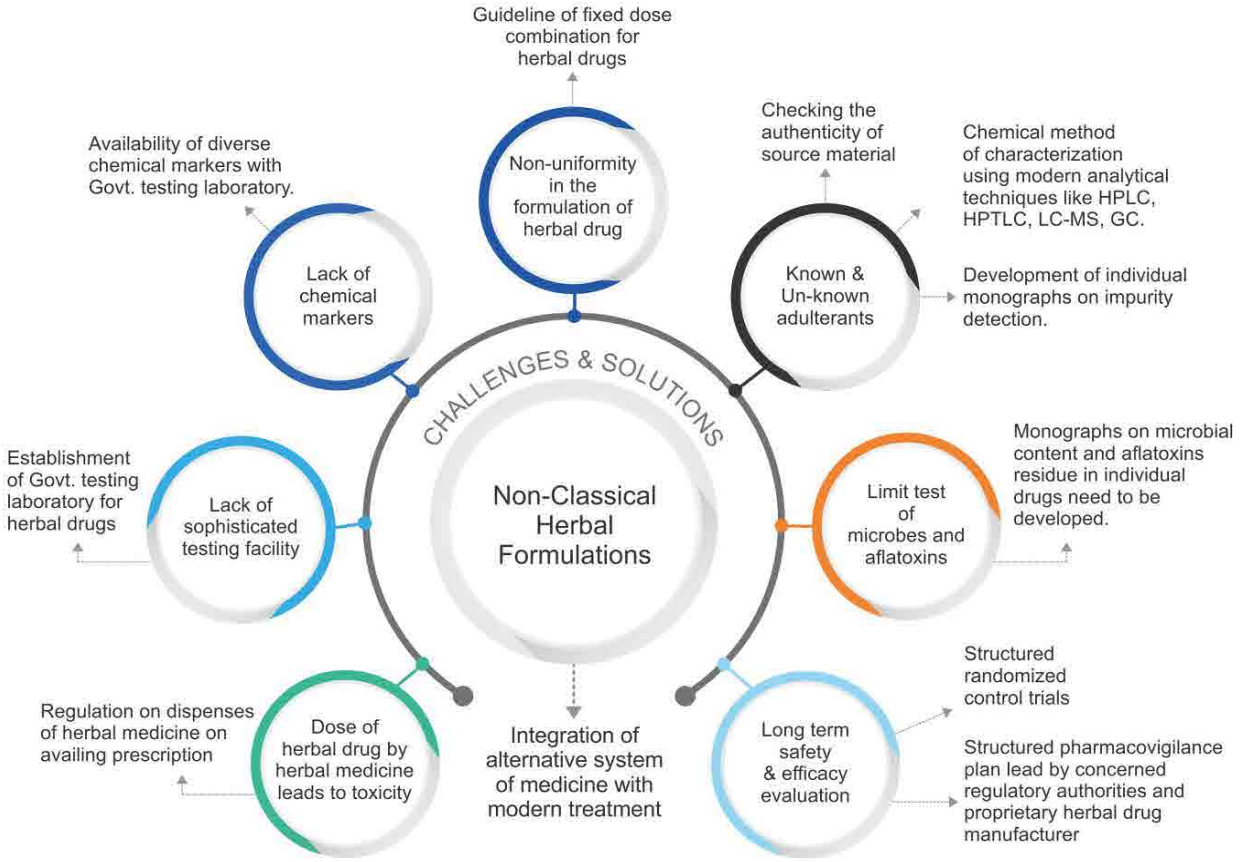

Fig. 1: Challenges and prospective solutions of non-classical herbal formulations

of these formulations leads to toxicity many a time[34,35]. Lack of a well-structured pharmacovigilance plan for herbal drugs is also a major flaw in establishing the long-term safety and efficacy for these formulations. Hence effort from the concerned regulatory authority and proprietary herbal drug manufacturer are required in addressing these challenges and integrating this system of medicine with the modern treatment.

Conflicts of interest:

There are no conflicts of interest.

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