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Formulation and Standardization of Herbal Medicinal Products: A Review of the Formulation Considerations, Quality Control and Safety of Herbal Products

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ABSTRACT

Herbal medicines are one of the complementary and alternative medicines used in the treatment of various ailments. In this review, we present on the aspects of formulation and standardization of herbal medicinal products in respect to the various considerations in formulating herbal products, quality control of herbal product formulations and materials, safety evaluation of herbal products and herbal product stability and shelf life determination. We argue that herbal products should be adequately controlled for pharmaceutical quality, to prevent contamination, substitution or adulteration of the plant material and to determine concentrations of potentially toxic constituents. Proper evaluation of existing data on traditional use, toxicological and clinical research as well as post marketing monitoring with an adequate system of pharmacovigilance should be adopted to enhance the rational use of herbal medicines and minimize potential health risks. Nevertheless, despite all efforts to provide safe herbal products, unexpected negative effects, which may inadvertently be considered idiosyncratic reaction, can never be prevented completely because herbal products in this respect are not different from conventional drugs. Quality control, safety evaluation and standardization may, however, minimize the chance of such adverse events occurring.

Keywords: Herbal medicine, Formulation, Standardization, Quality control, Medicinal plants

INTRODUCTION

The use of plants, animal parts and minerals as source of medicines predates historic times, being directed by human instinct, taste and experience of what was edible and not edible [1]. They distinguished natural materials and their combinations that had beneficial effects from those that were toxic and inactive through trial and error, employing a number of methods to yield consistent and optimal results. Consequently, these enabled them to meticulously gather information on herbs that have later guided development of well-defined pharmacopeias [2].

Today, countless number of herbs, herbal materials, herbal preparations and finished herbal products containing parts of plants and non-vegetable substances like cow ghee, honey, salt, milk, sheep's hair, vaseline, among others , have been exploited for their medicinal values[3]. The most commonly used parts of the plant are leaves, roots, seeds, flowers and barks, which are eaten, swallowed, drunk, inhaled, or applied topically to the skin[3].

Reports indicate that more than 80% of the world population particularly in developing countries depend on herbal medicines and products for healthy living, and a substantial proportion of the global drug market is accounted for by

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herbal products from both developing and developed countries, consumed as over the counter products, raw materials for the pharmaceutical industry and self-prescribed preparations of plant origin [4],[5].

There are approximately 60,000 plant species in sub-Saharan Africa, that constitute a quarter of the world's total, and only 83 of the world's 1100 leading commercial medicinal plants [6].This implies that there is less exploitation of abundant medicinal resources in Africa for commercial purposes, and the situation is partly accounted for by lack of standards to ascertain quality of medicinal plant materials and products that can be accepted in the world market. This review was undertaken to examine the challenges encountered in the formulation and standardization of herbal medicinal products in developing countries in respect to the various considerations in formulating herbal products, quality control of herbal product formulations and materials, safety evaluation of herbal products and herbal product stability and shelf life determination.

CLASSIFICATION OF HERBAL MEDICINE

According to WHO , a single medicinal plant may be defined as a food, a function food, a dietary supplement or herbal medicine in different countries, depending on the regulations applying to foods and medicines in each country[4]. These Herbal medicines can be presented as whole plant parts, crude extracts or finished pharmaceutical formulations like syrups, tablets, capsules, etc. 3]. These formulations may be classified as crude plant materials, herbal preparations and finished herbal products. The following is a presentation of scholarly definitions/ meanings of terms that apply to herbal medicines:

Crude plant material: This is any part of a plant e.g. roots, bark, leaves, floral parts, seeds fruits wood bulbs or plant exudates, or juice that has been harvested for use as a medicament [4].

Crude plant preparation: This refers to a plant or mixtures thereof that have been made into dosage forms without undergoing any extraction or purification process [4].

Finished herbal products: This is any preparation of crude herbal extracts whose active principles have not been separated into chemical entities [8]. Finished herbal products consist of herbal preparations made from one or more herbs. If more than one herb is used, the term mixture herbal product can also be used. Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture products to which chemically defined active substances have been added, including synthetic compounds and isolated constituents from herbal materials, are not considered to be herbal. They include waters, syrups, tablets, capsules, ear drops [8].

Herbal Based Drugs: This is any preparation whose active ingredient has been isolated from the plant and characterized chemically. Examples of herbal based drugs include: digoxin from the foxglove, quinine from cinchona bark, Codeine and morphine from the opium poppy) [9].

Herbal formulations: are dosage forms consisting of one or more herbs or processed herbs in specified quantities to provide specific nutritional, cosmetic benefits, and other benefits meant to diagnose treat, mitigate diseases of human beings or animals and/or to alter the structure or physiology of human beings or animals [10].

Herbal Preparations: Herbal preparations are obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates [7].

Herbal Substances: These include mainly whole, fragmented or cut plants, plants parts, algae, fungi, and lichen in an unprocessed, usually dried form but sometimes fresh. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system that records genus, species, variety and author [7].

VARIOUS CONSIDERATIONS IN FORMULATING HERBAL PRODUCTS

The purpose of development of herbal formulation is to provide the synergistic, potentiated, agonistic or antagonistic pharmacological agents within themselves and work together in a dynamic way to produce maximum therapeutic efficacy with minimum side effect [8].

There are numerous factors that should be considered during herbal medicine formulation. During formulation, it is important to begin with the disease in mind and any symptoms associated with the disease. With the disease clearly identified and symptoms understood, the focus of formulation therefore should turn to the identification medicinal plants that relive the condition and symptoms [11]. The challenge during the formulation of herbal products at this stage is making wrong disease diagnosis due to lack of diagnostic services resulting in making formulations for the wrong disease. Even after the right diagnosis has been made, most herbs do not have marker compounds that can easily be used to fully standardize the herbal remedies. The markers serve to calculate the quantity of herbal substance or active principles in the herbal medicinal product if the markers have been quantitatively determined in the herbal substance or herbal preparations [4]. The first selected herb should address the primary action needed and another should be selected as well to treat the symptoms presenting in the disease. This is known as secondary herbal action and provide additional support and are always in lower doses to alleviate symptoms of the

disease. In some cases, a synergistic herb/plant may be added to boost the action of the primary herb.

Furthermore, it is important that during formulations the choice of suitable dosage form is adequately addressed as it affects the efficacy and cost of the herbal medicine. This can be tinctures, decoction, infusion (teas), powder and glycerite [5]. Tinctures are generally more expensive than infusions and decoctions as it involves the use of other ingredients like alcohol. The challenge at this stage is quantification of herbal remedy. With conventional medicines, well designed clinical studies are conducted and animal experiments conducted to come up with reliable pharmacological parameters such as LD_{50}, TD_{50} and therapeutic index that guide in establishing the dose [12]. In herbal formulations, this is mostly based on preclinical evaluations, sharing experiences and consulting with other herbalists/ community members for those herbs that do not have documented dosages.

After establishing the dosage form, an appropriate dosing interval should be established. In determining the dosing interval, the age, body composition and lifestyle of the patient should be considered [11]. Children require lower dosages, thinner individuals usually respond to small doses, while those with big weight can tolerate higher dosing. Although teas are easy to prepare, it is important to determine for example whether someone will have time to make it three times in a day, otherwise powder and tinctures are much more convenient to take.

Another consideration should be made on safety of the herbal formulation. Although herbal medicine is considered safe due to the long history of use, it is important to consider contraindications for the use of some herbal group of individuals for example in cases of pregnancies and allergies [4]. Keen interest should be put on the potential for interaction with other herbal medicine and conventional medicine as well. However, the challenge is that little study has been conducted to evaluate the interaction of various herbs and other medicinal products. More still, lack of knowledge and skills in traditional medicine in developing countries coupled with poor pharmacovigilance practices further exacerbate the situation [3].

Last but certainly not least, shelf life and storage conditions should be considered. Appropriate formulation should ensure that the formulated drug can be safely used for the period of time its intended to be taken without deteriorating as well as maintaining its quality and efficacy [10]. For example, aromatics should be stored in airtight and ultraviolet protected glass to maintain its purity and freshness. This deep ultra violet glass is thicker, more durable than standard glass containers and blocks out UV light, since the jar lid systems are completely airtight [8]. The small glass bottles are perfect for herbal tinctures and come in several sizes (5-100ml) for easy carriage for daily use. These are ideal storage containers for herbs (or spice mixes, coffee, herbal salves, oils) and a great way to extend the shelf life of more perishable formulas, especially teas and powders [10].

We recommend the following steps as a guide for formulation of herbal medicinal products:

i. Look up literature on target disease/problem - Definition, etiology, risk factors, clinical course, clinical presentation-signs and symptoms, complications. Signs and symptoms for clinical diagnosis and how management is done - conventional and alternative therapies. Management should include pharmacological and non-pharmacological preventive measures and treatment. The treatment should state the drugs, dosage form, dose, dosing interval and duration, monitoring parameters, patient counseling on administration, side effects, drug interractions, missed doses and contra indications. Traditional methods of managing the disease/ condition should be pointed out. The plant materials /parts used, the bioactive extracts, dosage used, source/reference should be summarized in a table form.

ii. Review the selected plant material(s) included in the formula-Look up information in published journals, ethnobotanical surveys, dissertations/thesis in libraries, contact herbalist or community members. Ensure you obtain information on the Taxonomic classification (authority, division, sub division, sub order, order, family name, species), synonms, common names, morphological description, natural habitat, geographic distribution, biophysical limits, propagation methods, active chemical constituents, medicinal uses and dosage.

iii. Review the pharmacological profile of the selected plant materials in managing the disease/condition chosen.

Look up the nature of extracts used, efficacy in the laboratory and clinical setting (look up effective concentrations), safety-acute toxicity, sub-acute, chronic toxicity, any drug interractions reported in literature. Look at whether there are any reported interactions with food, conventional drugs, herbs and other disease conditions. Look up the active ingredients responsible for the activity to be studied, look up whether the active ingredients responsible for the activity you are to study are known or not, check whether bio-activity of plant extracts to be used in your formuala are known or not.

iv. Check out any information on half-life of your extract(s) to guide in determining frequency of administration to ensure effective plasma levels, biological half-life-check rate of bioactivity, check how long the effects last.

v. Review the dosage form you intend to prepare-This should include: Advantages and disadvantages, method(s)/procedure of preparation, key equipment required, quality control, packaging, stability issues-shelf life determination, storage, preservatives to use etc., labeling.

vi. Preservation of herbal medicinal products-how is it done and recommended amounts.

vii. Review pharmacological profile of the positive control drug to be used in the study.

The formula should have active ingredients and excipients with proper justification. Consider suitable dosage form and proper packaging of the product.

CHALLENGES ASSOCIATED WITH QUALITY CONTROL OF HERBAL PRODUCT FORMULATIONS AND MATERIALS

Most herbal product labels often cannot fully reveal what is in the container. Studies show that consumers have less than a 50% chance of actually getting what is listed on the label, and there are significant differences between what is listed on the label and what is in the bottled products [13]. It is therefore not a guarantee that the word "standardized" on a product label is an assurance of higher product quality, since there is no legal definition of the word "standardized" [14]. Consumers are often faced with the burden of deciding what is safe and effective for them and the lack of consistent labelling on herbal products further exacerbates the extent of consumer frustration. It is good practice for manufacturers of herbal products to provide information such as "the product has been manufactured according to approved standards," listing active ingredients, amounts, dosage and frequency of intake of the drug on the label.

Standardization of herbal medicines refers to the process of prescribing a set of standards or inherent characteristics, constant parameters, definitive qualitative and quantitative values that carry an assurance of quality, efficacy, safety and reproducibility [15]. It is the process of developing and agreeing upon technical standards. Specific standards are worked out by experimentation and observations, which would lead to the process of prescribing a set of characteristics exhibited by the particular herbal medicine [16]. Hence, standardization is a tool in the quality control process. Quality control and standardization of herbal medicines involve several steps. Clearly put, the plant source, quality of raw materials, processing and storage which are of great importance in guaranteeing the quality and stability of herbal preparations [4]. Additionally, factors such as the use of fresh plants, temperature, light exposure, water availability, nutrients, period and time of collection, method of collecting, drying, packing, storage and transportation of raw material, age and part of the plant collected, etc., can greatly affect the quality and consequently affect the therapeutic value of herbal medicines [14]. Some plant constituents are heat labile and the plants containing them need to be dried at low temperatures [15].

Also, other active principles are destroyed by enzymatic processes that continue for long periods of time after plant collection [16]. This explains why frequently the composition of herbal based drugs is quite variable.

As mentioned earlier, apart from these variable factors, others such as the method of extraction and contamination with microorganisms, heavy metals, pesticides, etc., can also interfere with the quality, safety and efficacy of herbal drugs [17]. For these reasons, pharmaceutical companies prefer using cultivated plants instead of wild-harvested plants because they show smaller variation in their constituents. Furthermore, and certainly more relevant, when medicinal plants are produced by cultivation, the main secondary metabolites can be monitored and this permits definition of the best period for harvesting [18].

The recent advances which occurred in the processes of purification, isolation and structure elucidation of naturally occurring substances have made it possible to establish appropriate strategies for the analysis of quality and the process of standardization of herbal preparations in order to maintain as much as possible the homogeneity of the plant extract. Among others, thin-layer chromatography, gas chromatography, high performance liquid chromatography, mass spectrometry, infrared-spectrometry, ultraviolet/visible spectrometry, etc., used alone or in combination, are are playing important roles in standardization and quality control of both the raw material and the finished herbal drugs [9].

The process of assuring material of reasonable consistency involves careful production and selection of raw materials and the processes employed in product manufacture. These controls, along with sections on examinations and tests, documentations and records, product types and their development, are in a white paper, which should aid companies in their considerations of GMP (Good Manufacturing Practice) requirements for botanical products [17]. According to WHO, the following tests can be used in assessing herbal product and material quality [4]:

- Macro and microscopic examination: Used in identification of right variety and search of adulterants.
- Foreign organic matter: This involves removal of matter other than source plant to get the drug in pure form.
- Ash values: These are criteria to judge the identity and purity of crude drug - Total ash, sulphated ash, water soluble ash and acid insoluble ash etc.
- Moisture content: Checking moisture content helps reduce errors in the estimation of the actual weight of drug material. Low moisture suggests better stability against degradation of product.
- Extractive values: These are indicative weights of the extractable chemical constituents of crude drug under different solvents environment.

- Crude fiber: This helps to determine the woody material component, and it is a criterion for judging purity.
- Qualitative chemical evaluation: This covers identification and characterization of crude drug with respect to phytochemical constituent. It employs different analytical technique to detect and isolate the active constituents. Phytochemical screening techniques involve botanical identification, extraction with suitable solvents, purification, and characterization of the active constituents of pharmaceutical importance.
- Chromatographic examination: Include identification of crude drug based on the use of major chemical constituents as markers.
- Quantitative chemical evaluation: To estimate the amount of the major classes of constituents.
- Toxicological studies: This helps to determine the pesticide residues, potentially toxic elements, safety studies in animals like LD_{50} and Microbial assay to establish the absence of toxins.

Despite the advances in standardization of herbal formulations, various challenges have been identified in quality control of herbal products and materials. First and foremost, issues of adulteration of herbal products and materials have been highlighted in several studies [4]. This involves mixing or substituting the original drug material with other spurious, inferior, defective, spoiled, useless other parts of same or different plant or harmful substances or drug which do not conform with the official standards. This is possible because herbal drugs are usually mixtures of many constituents and the fact that active principles are, in most cases unknown. Adulteration may occur as a result of direct or intentional adulteration and also by indirect or unintentional adulteration [19]. For example, a study, found that nutmeg was adulterated with basswood and prepared to the required shape and size, the colored paraffin wax was used in place of beeswax [17]. Sometimes, there is substitution with inferior quality material e.g. Belladonna leaves are substituted with Ailanthus leaves, papaya seeds to adulterate *Piper nigrum*. In some instances, there has been adulteration with harmful or fictitious substances e.g. pieces of amber colored glass in colophony, limestone in asafoetida, lead shot in opium, white oil in coconut oil, cocoa butter with stearin or paraffin. Moreover, numerous research studies have also documented the adulteration of powders e.g. powdered liquorice or gentian admixed with powder olive stones, under the name of cinchona [18].

Another challenge in the quality control of herbal products and materials is the faulty collection of herbal materials and the variations in the source of the raw material [15]. This is largely because plant materials are chemically and naturally variable and also because chemo-varieties and chemo cultivars exist. Inter- or intra- species variation in constituents is mostly genetically controlled and may be related to the geographical location. Sometimes, the quality of herbal ingredient can be affected by environmental factor like climate, altitude and other conditions under which it was cultivated [4]. In some cases, the optimum time of harvesting should be observed as it is known that the concentrations of constituents in a plant can vary during the growing cycle or even during the course of a day [4]. Further more active constituents usually vary between plant parts and it is not uncommon for herbal ingredient to be adulterated with parts of the plant not normally utilized [15]. In addition, plant material that has been previously subjected to extraction and is therefore 'exhausted' is sometimes used as adulterants to increase the weight of a batch of herbal ingredient.

Non-removal of associated structures e.g. stems are collected with leaves, flowers, fruits. Non-removal of undesirable parts or structures e.g. cork not removed from ginger rhizome.

Proper drying conditions should be adhered. Improper drying may lead to unintentional adulteration e.g. if digitalis leaves are dried above 65°C decomposition of glycosides by enzymatic hydrolysis [15].

The methods of harvesting, drying, storage, transportation and processing (for example, mode of extraction and polarity of the extracting solvent, instability of constituents, etc.) also affect herbal quality [20]. At present, no official standards are available for herbal preparations. Selective analytical methods or reference compounds may not be available commercially. Those manufacturers, who are currently doing some testing for their formulations, have their own parameters, many of which are very preliminary in nature. Presently, it is very difficult to identify the presences of all the ingredients as claimed in a formulation. The situation is even far more difficult for finished herbal products as it is not possible to conclude that all plants or starting materials have been included in the mixed product [12]. Hence, the first important task is to evolve such parameter by which the presence of the entire ingredient can be identified, various chromatographic and spectrophotometric methods as well as evaluation of physicochemical properties can be tried to evolve pattern for identifying the presence of different ingredient [13]. Wherever possible these methods can be applied for quantitative estimation of bioactive group of compounds like alkaloids, flavonoids, polyphenolic components or estimation of particular compound [5]. Deterioration happens especially during storage, leading to the loss of the active ingredients, production of metabolites with no activity and, in extreme cases, the production of toxic metabolites. Physical factors such as air (oxygen), humidity, light and temperature can bring about deterioration directly or indirectly. Post-harvesting factors:

Storage conditions and processing treatments can greatly affect the quality of herbal ingredient [13]. Inappropriate storage after harvesting can result in microbial contamination and processes such as drying may result in a loss of thermo-labile active constituents.

CHALLENGES IN SAFETY EVALUATION OF HERBAL PRODUCTS

Herbal medicinal products are perceived by the public as being more effective on certain health conditions, relatively low risk and safe compared to western medicine [21]. However, many reports have suggested an increase in the number of patients experiencing negative health consequences from the use of herbal medicines in recent years [22]. Numerous cases of poisoning have been reported in the literature leading to abdominal pain, vomiting, severe anemia, peripheral neuropathy and psychological disturbance [23]. These adverse events may be a result of several factors that include but not limited to the following: Adulteration of herbal products, undeclared medicines, wrongful identification of plant species, over dosage, misuse of herbal products by herbal practitioners, consumers and concomitant consumption with allopathic medicines [12]. Consumption of herbal products with foreign contaminants such as infectious microbes and toxic substances like heavy metals and pesticides is of particular concern and ought to be controlled [4]. Its therefore important to note that, the safety of herbal products cannot be guaranteed as most of the products are usually consumed as self-medication putting the life of consumers at risk due to inappropriate use [12]. Despite these upheavals, dispensing and use of these products is rampant in Uganda[3]. With weaknesses in regulatory infrastructure and lack of universal quality standards for herbal products, quality and safety of these products is rarely done in low income countries such as Uganda. Thus, the risk of consumption of toxic herbal products is elevated in low resource settings. Although, therapies involving these agents have shown promising potential with the efficacy of a good number of herbal products clearly established, many of them remain untested and their use are either poorly monitored or not at all [23]. The majority of adverse events reported in relation to the use of herbal products are attributed to poor quality of the product. It is also common knowledge that the safety of most herbal products is further compromised by lack of suitable quality controls, inadequate labeling, and the absence of appropriate patient information [24].

Most herbal products are considered safe due to their long history of use in the prevention, treatment and control of various diseases [25]. In such cases, the use of toxic plant ingredients has already been largely eliminated and reports of toxicity may be largely due to misidentification and overdosing of certain constituents. However, when there is no documentation of long historical use of herbal medicine, or when doubts exist about its safety, additional toxicity studies should be performed.

Medicinal plant toxicity may be attributed to the inherent toxicity of plant constituents and ingredients as well as manufacturing malpractice and contamination [4]. The absence of any reported or documented adverse events is not an absolute assurance of safety for herbal medicines. It is therefore imperative to conduct a full range of toxicological studies to examine effects that are difficult or even impossible to detect clinically. Some of these tests include genotoxicity, immunotoxicity, carcinogenicity and reproductive toxicity [25]. The tests can be *in vitro* to reduce the number of *in vivo* experiments. Common techniques used to study safety of herbal medicine are cell line techniques, micro-array and standardization techniques to adequately model toxicity. All the tests should be conducted ethically in accordance with WHO's research guidelines for evaluating safety and efficacy of herbal medicine products.

A number of studies have been conducted to uncover the toxic effects of herbal compound in the body. However, several shortfalls have been identified in the evaluation of safety of these herbal products. First and foremost, herbal medicine contains a vast number of chemically rich and complex compounds that are not easily isolated into single compound [24]. This is further compounded by the fact that plant phytochemicals are affected by several factors including geographical region, edaphic factors, plant genotype, part used harvesting, processing and storage condition.

Another important challenge in assessing safety of herbal products is that most medicinal plant trial drug has to be tested for batch-to-batch uniformity of the active constituents. In clinical trials, it is very difficult to have active and control groups with identical color, smell and taste of the herbal drug, which cannot be imitated while manufacturing a placebo.

Additionally, effective national pharmacovigilance program encourages the reporting of all suspected adverse reactions to drugs and other medical substances including herbal, traditional, or alternative remedies. Presently, there is lack of an effective pharmacovigilance system for herbal medicines in Uganda [3].

The issues of mixtures and deviation from conventional pharmacological approaches remain a major problem, along with the consequences of using the wrong source plants or ingredients, variable content of active constituents and a narrow therapeutic window with herbal medicines [12]. Concurrent contamination with any one of the toxic metals, bacteria, viruses, or pesticides may also occur.

HERBAL PRODUCT STABILITY AND SHELF-LIFE DETERMINATION

Stability testing of herbal products is a complicated issue because the entire herb or herbal product is regarded as the active substance, regardless of whether constituents with defined therapeutic activity are known [4]. Herbal products undergo changes, depending on the way that they are harvested, processed, manufactured and stored. Stable drug product maintains their identity, strength, therapeutic effect within given specifications throughout the shelf life [6]. Several factors have been shown to affect the shelf-life of the formulations, related to manufacturing processes and environmental conditions. These factors include; heat (temperature during storage), moisture (inherent moisture and moisture absorbed during storage), exposure to light, exposure to oxygen (air) and exposure to microbes (storage in unhygienic packs/conditions and ingress of air into pack) [15]. The purpose of a stability testing is to provide proof on how the quality of the herbal products varies with time under the influence of environmental factors such as temperature, light, oxygen, moisture, other ingredient or excipients in the dosage form, particle size of drug, microbial contamination and trace metals.

Different approaches have been proposed for the standardization of herbal products such as activity-based standardization and determination of the biologically active compound [15]. The activity-based standardization is based on the inhibition of activity of a particular enzyme related to the disease. The concentration of the herbal drug required to inhibit 50% of a fixed amount of enzyme activity is termed the IC_{50} value for enzyme inhibition [27]. Thus, under defined conditions, herbal drug should give a fixed IC_{50} value for enzyme inhibition. If the IC_{50} values are reproducible, the assay can be reliably used in the activity-based standardization of the said herbal drug. The results of a study on Triphala powder suggested that as the powder ages, it loses potency with respect to its ability to inhibit hyaluronidase and collagenase enzyme activities [27].

The bioactivity and the concentration of the active compound in the drug may be assessed at various intervals of time to determine the shelf life and expiry date of the drug. However, this method may be applicable in case of single drugs only. It is recommended that in case of a herbal medicinal product containing a natural product or a herbal drug preparation with constituents of known therapeutic activity, the variation in component during the proposed shelf-life should not exceed ± 5% of the initial assay value, unless justified [4]. WHO has set certain standards for herbal drugs. These parameters may be assessed at different intervals of time and the changes noted, so as to determine the time when the drug loses its characteristic properties.

Some would expect herbal medicine formulation to be studied for their stability using typical pharmaceutical approaches for single chemical entity drugs, where not more than 10% deterioration of the active molecule occurs when it is stored at conditions that the manufacturers recommend. This approach is neither suggested nor recommended for herbal formulations for the following reasons:

- Active chemical molecules in the herbal medicine product formulations are inadequately known and markers, which are currently used, do not necessarily reflect a true correlation with biological activity.
- Formulations, even if based on single herbs are multi-component in terms of chemical constituents.
- Assaying a single marker is against the principle of the holistic approach of therapy of herbal medicine formulations, as it is difficult to pinpoint that the entire health benefit of herbal medicine is caused by one such compound identified.

In such formulations it is extremely difficult to specify an expiry date (a date after which the potency of the actives would be lost or reduced to sub potent levels), so it is preferable to evaluate a ‘best before’ date [4]. This is the date after which one or more properties of the formulations would have shown considerable changes, perceived by the consumers and leading to doubts about the quality of the formulation and hence its efficacy. Taking into account these special features of herbal medicine, adequate quality concepts have been established. As part of a total control strategy for herbal substances, herbal preparations and herbal medicine, a set of test criteria including qualitative and quantitative parameters has been recognized as quality or 'indicator' [28]. With regard to stability tests, chromatographic fingerprints as well as appropriate methods of assay via marker substances represent the fundamental part of this concept, laid down in shelf-life specifications [28]. Notwithstanding the appropriateness of this approach, its realization is often associated with analytical problems and high costs. In summary, herbal medicines have a number of characteristics that clearly differentiate them from chemically defined medicinal products and therefore specific stability guidance needs to be established, which covers particular aspects that existing specific herbal guidelines and general guidelines on stability do not address.

CONCLUSION

Herbal medicine is considered important but underutilized tool in the transformation of healthcare in developing countries. This is largely due to a myriad of shortcomings ranging from insufficient and unacceptable evidences of safety, efficacy and standardization to inconsistent production practices. Standardization of herbal medicine therefore presents an important footstep towards providing consumers with reliable and safe herbal medicine products. This is necessary because neither all herbal products are harmless nor should the use of botanicals be unconditionally rejected as dangerous. Like all drugs, herbal products should be adequately controlled for pharmaceutical quality, to

prevent contamination, substitution or adulteration of the plant material and to determine concentrations of potentially toxic constituents. Proper evaluation of existing data on traditional use, toxicological and clinical research as well as post marketing monitoring with an adequate system of pharmacovigilance should be adopted to enhance the rational use of herbs and minimize potential health risks. Nevertheless, despite all efforts to provide safe herbal medicine products, unexpected negative effects, which may inadvertently be considered idiosyncratic reaction, can never be prevented completely because herbal products in this respect are not different from conventional drugs. Quality control, safety evaluation and standardization may, however, minimize the chance of such adverse events occurring.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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