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Herbal Drug Development from Traditional Formulations: Refocusing Pharmaceutics and Posology for Accelerated Validation

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Authors' contributions

This study was conducted in collaboration between all authors. Author SJA designed the study and wrote the first draft. Authors BKT, BUE and AAA reviewed the draft and managed the references. Authors MG, JA and KSG approved the study design and the draft manuscript. Authors SJA and JA finalized the manuscript. All authors read and approved the final manuscript.

Review Article

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ABSTRACT

Background: The World Health Organization (WHO) recommended that the toxicity data of a traditional medicine (TM) product that has been in use for 20 years or more without untoward effects should be determined, as the first step in its research and development

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(R&D). Such data in conjunction with efficacy data would be used to develop an appropriate dosage form of the product. A key objective in researching such a product is to validate the basis of the therapy, including the formula. Such validation, and any attempt to modernize the product, should be guided by an understanding of the traditional know-how. The Nigerian National Institute for Pharmaceutical Research and Development (NIPRD) utilized this approach in developing Niprisan, an antisickling drug, based on a TM product used since antiquity in Yoruba Medicine.

Aim: This article aimed to advocate the continuance and improvement of the WHO model of herbal drug research and regulation (HDRR) as the most logical approach for adoption by researchers and regulators.

Methodology: NIPRD's adoption of the WHO model since 1989 was reviewed in parallel with trends in herbal drug research worldwide; and within the contexts of regulatory practices by Nigeria's National Agency for Food and Drug Administration and Control (NAFDAC) and the European Medicines Evaluation Agency (EMEA), with a view to identifying more effective strategies within the WHO paradigm for HDRR.

Conclusion: Drug regulatory agencies (DRAs) like NAFDAC require effective laws, policies and quality management systems (QMS) to execute their mandates effectively. On the other hand, NIPRD's output depends upon proper actions by a seasoned and responsive DRA. Therefore, noting that NIPRD and NAFDAC were both created by military decrees in 1989 and 1992 respectively, rather than by parliament acts, it is recommended that in addition to instituting more effective laws and policies to regulate NAFDAC, both NIPRD and NAFDAC need to adopt and implement suitable QMS for self-regulation, eg: ISO 9001 for whole organizations; and ISO/IEC 17250 for the laboratories.

Keywords: Traditional medicine (TM); product; toxicity data; dosage form; research; development; regulation; drug regulatory agency (DRA).

1. INTRODUCTION

Herbal "pharmaceutics and posology" refers to the act of preparation and administration of a botanical dosage form. It is concerned with how much of a given herbal material is to be included in a dose, and how the dose is to be administered in a given clinical setting. It is a complicated task, made even more complex by the following realities:

- There is often too little data on the nature and amount of constituents in an herb
- There is usually a dearth of data on the mechanism of action of an herbal material
- Herbal materials vary greatly with season, geography, and method of harvest
- Herbal doses vary more with methods of preparation than do pharmaceuticals
- The core issues of "traditional-use registration" are often not understood by all

"Traditional-use registration" [1], also called "listing" by Nigeria's drug regulatory agency (DRA) – National Agency for Food and Drug Administration and Control (NAFDAC), is particularly important in emerging polities, or countries like Nigeria. This is because in these countries, the issue of "traditional use registration" is neither properly understood nor effectively addressed by regulators, such as NAFDAC. Owing to this deficiency, less important, or even peripheral issues, tend to dominate regulatory agenda, and thereby confuse the process for regulating TM products. Yet, as is well known, TM products still constitute a key factor in healthcare delivery in many countries worldwide [2,3]. It is important to note that since most TM products are taken orally, such products have, in the

US, since 1994, been called “dietary supplements” rather than herbal, or botanical medicines. This shift in nomenclature has also lately occurred in China. The use of the term “dietary supplements”, which avoids the use of the term “medicine”, proved semantically strategic in the passage of the “Dietary Supplements Health and Education Act (DSHEA) of 1994” [4]. Had the term “medicine” been used rather than “dietary supplement” there would have been a need to prove efficacy, which is not required by either the United States Food and Drug Administration (US-FDA) or the European Medicines Evaluation Agency (EMEA) for products that make no overt medicinal claim.

2. IMPORTANCE OF A PROPER REGULATORY AGENDA FOR TM PRODUCTS

As previously described [5,6] the importance of DSHEA, for example, may be discerned from the following: Since the signing of the DSHEA bill, the US, which indeed boycotted the Alma-Ata Declaration [7], became the topmost promoter of TM products. Before 1994, the turnover of TM products in the US was only in millions, but it has, since the late 1990s, been reckoned in billions of USD. India’s Ayurvedic Medicine (IAM) and China’s Traditional Chinese Medicine (TCM), or Kampo Medicine in Japan and Korea continue to flourish in these countries because these nations long ago addressed issues relating to “traditional-use registration” as a key piece of legislation [3,8,9]. The ever increasing use of TM products in Europe is largely accounted for by the political adjustment of the laws regulating herbal products in the European Union (EU) since 2004. It is also known that without the contribution of TCM, China would not have been able to bring the per capita healthcare cost down to a mere USD 7.00 in 2005 [3]. Therefore, the benefits of proper drug laws are all too obvious in developed polities. However, the same cannot be said of many immerging polities, where the laws regulating traditional remedies are either nonexistent or are out of synch with contemporary developments [3,5,6,8,9]. This article aims to address this serious lacuna that exists in many developing countries, using Nigeria as an example.

3. THE AIM OF THIS ARTICLE

In this article we describe in some depth the nature of the five realities outlined in the “Introduction”. We will expatiate on the WHO principle that: “long-term uneventful use of a TM constitutes an evidence of the TM’s safety and/ or efficacy”, and show how the principle has been applied in the development of Niprisan, Conavir – an immunostimulant, Niprd-AM1 – an antimalarial, and Niprifan – an antifungal. In these four cases the methods of preparation of dosage forms closely followed appropriate modifications of traditional practices. Earlier, it was reasoned that: “Once ethnobotanical survey or some other accepted practice (such as a valid observational study) has confirmed the merit of a given plant for a stated indication and preliminary *In vitro* or *In vivo* biological data are consistent with that indication and the material has passed WHO’s acute and chronic toxicity tests, the next logical action should be to standardize the plant material involved”. This approach involves:

- Establishing the plant’s taxon, including the name of the authority behind the classification system used.
- Establishing the part of the plant used and how it was collected.
- Taking due cognizance of the herbalist’s method for preparing the clinical sample.

To take “due cognizance of the herbalist’s method for preparing a clinical sample”, as we attempt in this article, is to attend to the five realities outline in the “Introduction”. These

collectively imply that products developed in accordance with the foregoing, which is consistent with the WHO approach should be considered for registration by DRAs.

4. TYPES OF HERBAL DOSAGE FORMS

Although the examples given in this article embrace only oral dosage forms (Niprisan, Conavir and Niprd-AM1) and one topical preparation (Niprifan), herbal dosage forms include inhalational and parenteral preparations (Table 1). A more elaborate discourse of herbal dosage forms is presented elsewhere [10].

Table 1. List of dosage forms with references to herbal medicinal products

Types of dosage form	Reference to corresponding herbal products
Oral • Powder • Granules • Capsule • Pastes • Solution • Suspension • Tablet	Herbal equivalents of the pharmaceutical dosage forms on the left are infusions or their derivatives (eg: tisanes), solutions (tinctures) or suspension (gruels). Tisanes or teas were the dosage forms of choice. In lands with long traditions of herbal medicine, infusions are the preferred dosage form. But herbs can also be incorporated in food, as peppers and curries are used in Africa and India. In China, patients receive large packets of herbs from TCM hospitals. These are used to make pots of infusions for consumption.
Topical 1. Ointments 2. Skin patch – is a medicated adhesive patch placed on the skin to deliver a specific dose of medication 3. Tincture 4. Others, eg: ear drops and eye drops	Ointments are smooth, greasy substances used on the skin to soothe soreness, itchiness, heal wounds, or make the skin softer Similar topical preparations with herbal equivalents include: • Balm –soothing, fragrant, oily resinous plant substances • Cream - medicinal preparation that has a thick smooth consistency like the fatty part of milk • Liniment - liquid rubbed into skin to relieve pain, eg: one containing alcohol and camphor • Lotion - a thick liquid preparation applied to skin for cosmetic or medical reasons
Inhalational • Aerosol • Inhaler • Nebulizer • Smoking • Snuff • Vaporizer	Aside from nebulizer, which are relatively recent, each device/ dosage form on the left column probably has a traditional equivalent or precursor of some sort, especially in the those traditional medical system like Ayurveda, TCM and Unani that benefited from early documentation of procedures. For example smoking is akin to vapor inhalation. Tobacco snuff, or shred *Cymbopogon* leaves are used to relieve cold symptoms in Nigeria
Parenteral These mainly include: 1. Intraperitoneal (IP) 2. Intravenous (IV)	3 Subcutaneous (SC) 4. Intradermal (ID) 5. Intramuscular (IM) But herbal equivalents are extremely rare even in IAM and TCM

Leaf and flower infusions are made by pouring one cup (approx. 250 ml) of boiling H_2O over 1-1.5 teaspoonful of herb and letting it to sit for 10-15 minutes. However, bark or root infusions need gently boiling for 10-15min [11]. Tinctures are alcoholic solutions of plant substances. Typical alcohol contents are: 25% for water-soluble constituents such as mucilage, tannins and some glycosides; 45-60% for essential oils, alkaloids, most saponins and some glycosides; and 90% for resins and oleoresins. The first commercially available prescription patch was approved by the US-FDA in December 1979. The patches administered scopolamine for motion sickness [12]. Skin patches are most probably a rarity even in IAM and TCM, but their overall commonsense and simplicity may suggest that traditional precursors might have existed

5. MULTIPLICITY AND VARIBILITY OF MATERIALS IN A PRODUCT

If a preparation like Niprisan, which is in high demand, is to be mass-produced, its production must conform to GMP, ie: the dosage form must exhibit consistency in appearance and effect. Such conformity must take into cognizance the inherent variability of biological materials. This means in formulating and producing the dosage form, the following actions must be considered and taken:

- Limits must be set for the starting materials (4 herbal items and a mineral – trona).
- Processes must be chosen such that efficiency is not at the expense of efficacy
- The manufacturing processes must be observable, measurable, and reproducible
- The finished product must pass relevant tests, including, where practicable, one directly related to the disease condition of interest.

To attend to the foregoing systematically and methodically, is to produce a dosage form as per GMP. The foregoing in the case of Niprisan is illustrated in (Table 2), which is taken from results presented elsewhere [13]. Ideally, GMP-production of herbal dosage forms should commence from the stage of cultivation, or from the stage of preparing/sampling of the required plant parts.

Table 2. Variability in LOD results of the five components of Niprisan

LOD % w/w	*P. guineense*	*E. caryophyllata*	*P. osun*	*S. bicolor*	Trona
Range	6.38–8.80	7.67–9.82	4.02 – 6.96	7.15–8.17	20.44–28.35
Mean ± SD	7.87±0.55 (n=18)[a]	8.67±0.50 (n=18)[b]	5.76 ± 0.36 (n=27)[c]	7.85±0.47 (n=7)[d]	21.80±0.88 (n=10)[e]
Mean ± 3SDs	7.87±1.65 (n=18)	8.67±1.50 (n=18)	5.76 ± 1.08 (n=27)	7.85±1.41 (n=7)	21.80±2.64
Range	6.21–8.94		3.94 – 7.03	3.20–4.42	16.90–18.50
Mean ± SD	7.84±0.66 (n=20)[a]	8.68±0.59 (n=20)[b]	5.74 ± 0.54 (n=28)[c]	3.59±0.27 (n=11)[d]	17.38±0.49 (n=8)[e]
Mean ± 3SDs	7.84±1.98 (n=20)	8.68±1.77 (n=20)	5.74 ± 1.62 (n=28)	3.59±0.81 (n=11)	17.38±1.47 (n=8)

Statistical test of the LODs above yielded the following results (a)-(e):

(a) Indicates that the difference between the LOD's of the two consignment or varieties of P. guineense is statistically insignificant.

(b) Indicates that the difference between the LOD's of the two consignments or varieties of E. caryophyllata is statistically insignificant.

(c) Indicates that the difference between the LOD's of the two consignments or varieties of P. osun is statistically insignificant.

(d) Indicates that the difference between the LOD's of the two consignments or varieties of S. bicolor is statistically significant at P<0.001.

(e) Indicates that the difference between the LOD's of the two consignments or varieties of trona is statistically significant at P<0.001.

The foregoing results and statistics are taken from Ameh et al [13], which followed the WHO approach [14,15]

6. STANDARDIZATION OF MATERIALS PRIOR TO INCORPORATION

An herbal substance is defined as a material derived from plant by extraction, mechanical manipulation, or some other process [15]. In herbological parlance each herbal material in its entirety is regarded as the active substance, even though the constituents may be a group of chemically defined entities acting cooperatively to achieve the pharmacological effects the medicinal plant [16]. The chemistry-manufacturing-control (C-M-C) profile of a product like

Niprisan [13-15], stems from, and focuses on the fact that herbal materials are prone to contamination by herbicides, pesticides, mycotoxins, and other chemical entities; and are subject to profound variations in physicochemical characteristics, such as loss on drying, extractability, and others. Hence, the more the number of herbal components in the dosage form, the more complex is the product's C-M-C profile [14]. The traditional recipe, from which Niprisan was developed, is an infusion of the seeds of *Piper guineense*; flower buds of *Eugenia caryophyllata*; stem parts of *Pterocarpus osun*; and the leaf stalk of *Sorghum bicolor*, in a local gin, containing trona. The recipe had been in use for ages in treating sickle cell crises among the Yoruba of Nigeria [17]. Since there are no specific assays, as yet, for Niprisan and its herbal components, it is essential for the suitability of each material to be confirmed with respect to the following key parameters:

- Botanical identity
- Loss on drying (LOD)
- Extractability in water, or other named solvents such as ethanol, ethylacetate, and hexane
- Total ash
- Acid-insoluble ash
- Any test designed to identify and quantify one or more phytochemical entities
- Any test designed to include or exclude a defined parameter, or activity.

The foregoing parameters are useful as quality control variables for monitoring production and hence to ensure a consistent dosage form. Thus a standardized herbal material is one whose quality control variables have been determined and confirmed to fall within a given range, or has been processed, where necessary and feasible, so that such variables fall within the accepted range. WHO [18] prescribed: Mean ± 3 SDs for at least 20 valid determinations. For example, if the LOD of a material is 11.00±0.37 %w/w (n=20) the acceptable range would be 11.00±1.11%w/w. Where necessary and sensible materials can be re-dried and retested to ascertain suitability. The term "standardized extract" refers to a dosage form that has been standardized with respect to a stated parameter, such as pH, or quantity of a named constituent of the herb.

7. PREPARATION AND SAMPLING OF HERBAL MATERIALS

7.1 Harvesting and Preparation of Plant Parts

Depending upon intended use, each plant part for preparing botanicals has an optimal time or condition for harvesting. The guidelines and comments indicated in (Tables 2-4) are applicable as prescribed by WHO [18,19] or by the herbalists, or traditional healers [20].

7.2 Setups/ Schemes for Pilot Scale Preparations of Dry Extracts

Schemes for preparing aqueous extractions and concentrating them are depicted in (Fig. 1), while the corresponding setups for non-aqueous extracts are depicted in (Plates 1 and 2). Once these schemes are found suitable, engineers can perfect the needed machinery and supporting process systems.

8. SAMPLING OF PREPARED PLANT MATERIALS

Special sampling procedures are especially required for medicinal plant materials because of their lack of homogeneity [18]. The questions that often arise are:

- What special handling procedures are required?
- Which parts of the plant are to be included in the sample?

Such questions are usually addressed as per WHO [18] as follows:

8.1 Sampling of Materials in Bulk

- Firstly, each container is inspected to ascertain conformity with prescribed packaging and labeling.
- Secondly, checks are made for damaged or poorly labeled containers, and where necessary these were sampled individually and separately.
- Thirdly, if the rest of the batch was uniform, containers are selected for sampling as indicated in Table 3.
- Fourthly, the selected containers are opened, and the contents are examined, with the aim of seeking out the features of interest.
- Fifthly, the following points/ actions are to be noted/ carried out in the actual act of sampling:
    - Three (3) original samples are taken from each container – top, middle and bottom.
    - The 3 original samples are combined into a pooled sample and mix carefully.

The average sample is obtained by quartering the pooled sample.

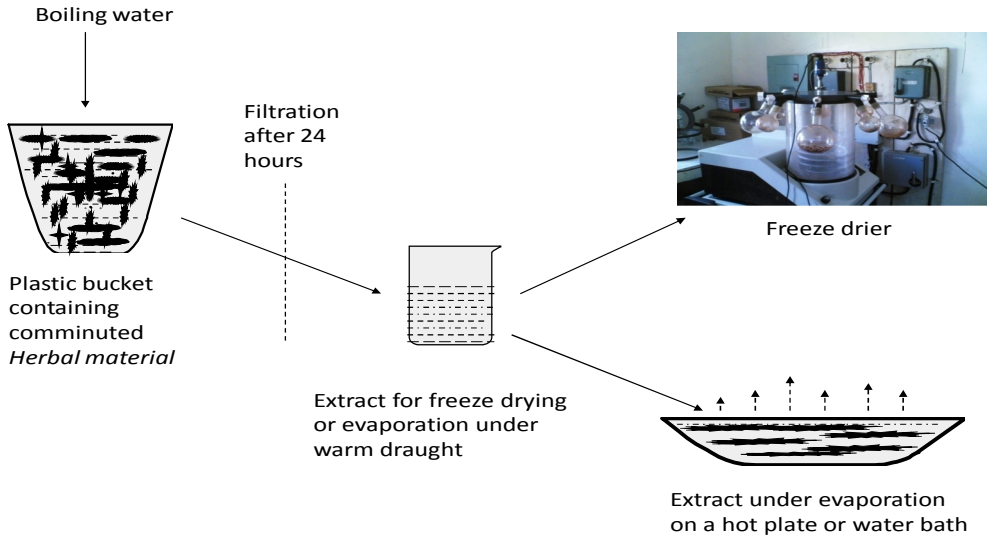

Fig. 1. Schematic for pilot preparation and concentration of an aqueous extract

The diagram above is self-explanatory. Boiling water is used to extract the comminuted plant material. This is followed by filtration, using a suitable method such as through muslin or filter press. The resulting solution may be freeze-dried or evaporated to dryness over a hot plate or water bath

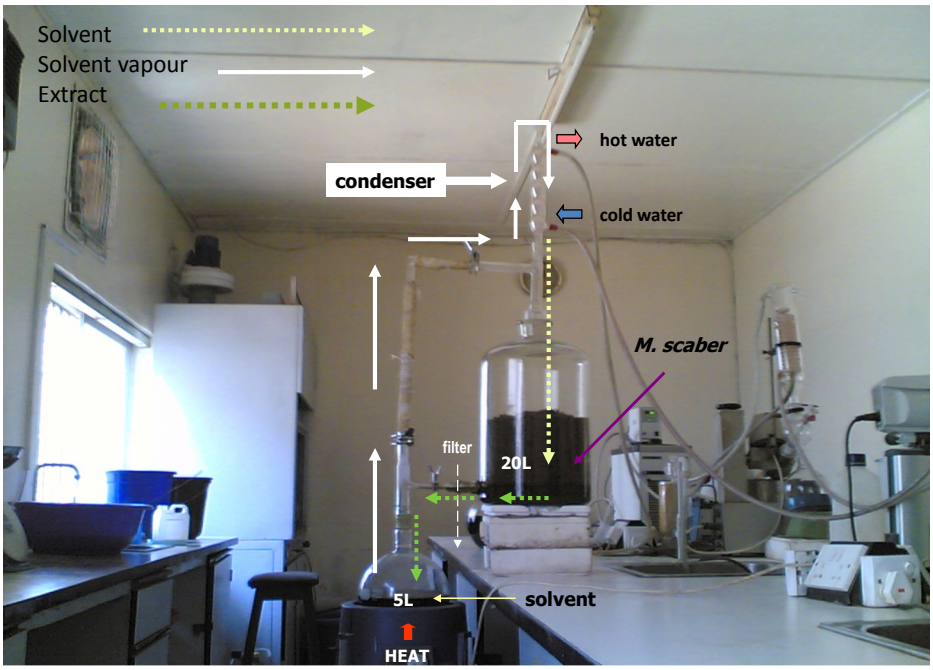

Plate 1. Setup for pilot scale preparation of *M. scaber* extract

The drug is extracted with ethylacetate. The solvent is placed in the 5L flask and recycled by heat and reflux into the 20L jar containing coarsely milled M. scaber. The system is allowed to run for 8-24 hours under close watch until extraction is complete judging from the appearance of the extract emerging through the filter. (When the emerging extract is colorless, extraction is deemed to be complete). The extract in the 5L flask is either transferred in bits at a time to an evaporating dish, subsequent to evaporation to dryness under a water bath, or it is subjected to further concentration using the setup in Plate 2

8.2 Quartering

Quartering consist of the following stepsas per WHO [18]:

- A pooled sample from original samples is mixed carefully and thoroughly, and constituted it into a square-shaped heap.
- The heap is divided diagonally into 4 equal parts, and any 2 diagonally opposite parts are selected and mixed carefully.
-

The process is repeated as necessary until the required quantity of sample is obtained. Any remaining material is returned to the batch or container as per WHO [18].

8.3 Final Samples

- Final samples are obtained from an average sample by quartering, as described above. This means that an average sample results to 4 final samples.

Each final sample is divided into 2 portions - one portion is retained as reference material, while the other is tested as per WHO [18].

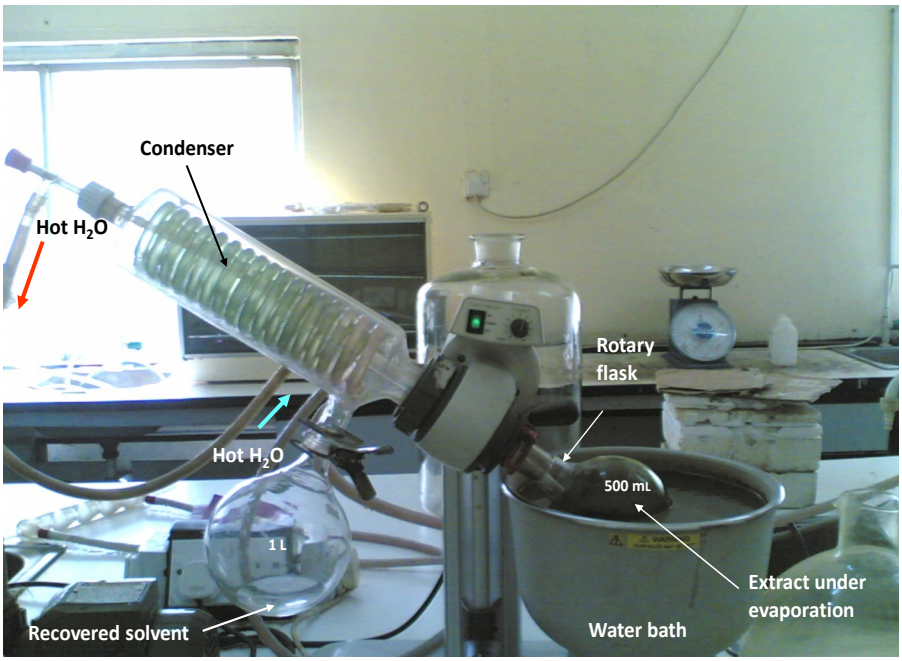

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Plate 2. Setup for pilot scale concentration of *M. scaber* extract

Aliquots of extract from the setup described in Plate 3.1 are transferred to the 500-ml flask above. The extract is concentrated by evaporating off the solvent, which is subsequently recovered as shown above. The concentrated extract is finally transferred to an evaporating dish and evaporated to dryness under a water bath

8.4 Establishment of Limits

- Where possible or necessary analytical results from 20 successive batches are pooled together, and the grand mean and "three sigma limits" (± 3 Standard Deviations) are calculated, to represent established limits as per WHO [18].

9. HERBAL QUALITY CONTROL/ GOOD MANUFACTURING PRACTICE (GMP)

9.1 List of Select Tests Relevant to Herbal Quality Control/ GMP

Detailed procedures and the results of tests listed and exemplified in (Table 7) were according to WHO [18] as described previously [21,22].

Table 3. Guidelines on harvesting/collection of flowers, whole plants and roots

Plant part	Condition for harvesting/ collection, with pertinent comments
Flowers: Flowers are: • Sometimes colored and/ or scented part of an Angiospermae (a flowering plant) that contains its reproductive organs • The most enduring characteristic of Angiosperms, and are often the most delicate part of an herbal harvest A flower typically consists of a leafy shoot with modified leaves, petals, and sepals, surrounding male or female organs, stamens, and pistils.	Flowers are the most delicate part of an herbal harvest because they can perish or decay faster than other plant parts, especially in warm and damp enclosures. Consequently, it best observe/ do the following: • Collect flowers during the middle of the day, and especially on a day that is dry. • Avoid any flowers that have any amount of damage or decay, and do not collect spent flowers. • Once picked, move the flowers from the harvest container, to your drying area as quickly as possible to avoid bruising. The foregoing applies to full-blown flowers. However in some plants, such as clove (*Eugenia caryophyllata*), the flowers are harvested long before they mature, ie: as flower buds. Scented flowers contain biologically active aroma compounds or essential oils.
Whole plant: It is quite common to use whole small plants or herbs in herbal preparations, but the following key points must be noted: • The term “aerial parts” is used if roots are excluded • If the roots are included the term “whole plant with roots” is used	Herbalists often recommend: Just before the plant flowers • This implies a fair knowledge of the plant’s ecology and habits • Most herbs harvested by cutting off most of the aerial parts may not regrow The foregoing are essential for good agricultural and collecting practice (GACP). As a rule, when harvesting the majority of plant growth in one area, some plants must be left intact for propagation. In the case of wild growth, if the whole plant is needed, the recommended practice is to harvest no more than 1/3 of the plants [19,20].

Depending upon intended use, each plant part for preparing botanicals has an optimal time or condition for harvesting [18,19] or prescribed by herbalists, or traditional healers [20]

Table 4. Guidelines on harvesting/ collection of leaves, bark, fruit an seeds

Plant part	Condition for harvesting/ collection, with pertinent comments
Leaves: Leaves are the most commonly used plant parts. The following notes are useful: • The best time for harvesting or picking leaves depends upon the intended purpose as enumerated in the left column. For example leaves desired for their volatile oils should be picked at the time they are expected to be most flavorful Generally leaves are most flavorful when the plants are in the growth stage	Leaves to be used as leafy vegetables/ fresh leaf tea • Such leaves can be plucked any time during the herb's growth. • If shed leaves are required, they should be picked when they fall Such leaves as above should be used immediately Leaves required dry: • Should be collected in the morning after the dew has dried, but before the heat of the sun peaks - this ensures maximum volatile oil contents • Should be harvested young, and as often as necessary, since leaves most flavorful when plants are in growth. Other conditions: Leaves from the evergreen herbs (eg: rosemary and thyme) should be harvested just before flowering for the most flavor.
Bark: Bark harvesting is most often of large plants, ie: trees or shrubs. Since the practice can cause plant death, it must be done with utmost care. In particular, barks are never to be peeled in a full circle round branch, as such causes plant death.	Bark harvesting as per GACP requires the following conditions: • Damp, rather dry conditions • Only minor branches, rather than the trunk is selected • Bark harvesting must be done as sparingly as possible, preferably with young rather than old plants • Bark harvesting can be done on felled trees, but this may be true for tree killed by disease or lightening.
Seeds and Fruit: A seed is a plant part produced by sexual reproduction. It contains the embryo that gives rise to a new plant. In Angiosperms the seed or seeds are enclosed within the plant part called fruit.	The following are to be observed/ or done when harvesting seeds or fruit: • Ensure the seeds are ripe – this may require sampling • Choose a dry day, just before the seed is ready to be dispersed – this requires knowledge of the plant's habits. Seeds are particularly difficult to harvest, because they require a lot of patience and frequent monitoring to avoid harvesting too early

A fruit is the seed-bearing part (the ovary) of a plant. It may be succulent, bearing one or more seeds (like a mango or guava fruit), or it may be non-succulent, like chestnut (a true nut in the botanical context) or like peanuts (a nut only in culinary context)

9.2 Examples of Application of Select Tests to Select Products

9.2.1 Niprd-AM1

Niprd-AM1 is the dry water extract of the root of *Nauclea latifolia* (NL). The dry extract is anti-malarial, and is described as active crude extract (ACE); while NL, which is referred to as crude herbal drug (CHD), is a coarsely comminuted material that can be decocted to yield anti-malarial tisane. (Tables 5 and 6) show results obtained with NL and Niprd-AM1 as described previously [21,22].

9.2.2 Niprifan

Niprifan is the dry ethylacetate extract of aerial parts *Mitracarpus scaber* (MS). The dry extract is anti-fungal, and is described as active crude extract (ACE); while MS, which is referred to as crude herbal drug (CHD) can be macerated or finely cut and applied to the skin. (Fig. 2) and (Table 7) show results obtained in the GC-MS study of Niprifan as described previously [22].

9.2.3 Conavir

Conavir is the dry water extract of aerial parts of *Andrographis paniculata* (AP). The dry extract is immune-stimulant/ anti-HIV, and is described as active crude extract (ACE); while AP, which is referred to as crude herbal drug (CHD), is a coarsely comminuted material that can be decocted to yield an immune-stimulant/ anti-HIV tisane. (Table 5) shows results obtained with NL and Niprd-AM1 as described previously [21,22].

Table 5. Sampling of materials in bulk as per WHO

Number of containers/batch	Number of containers to sample	Remark
• 1 – 5	• Each	• -
• 6 – 50	• 5 selected at random	• -
• 51 and above	• 10% selected at random	• 51 is treated as 60

From the foregoing 61 is treated as 70, and 71 as 80, and so on, as per WHO [18]

Table 6. Features to look for in samples supplied in bulk

General characteristic	Specific example of characteristic
• Organoleptic	• Color, texture, taste, or odor
• Form of presentation	• Raw, cut, crushed, or compressed
• Presence of admixture/ foreign matter/ mould/ signs of decay.	• Sand, glass particles, or dirt. Fungi (eg: *Aspergillus*) should be excluded
• Presence of insects.	• The type found maybe a significant finding.
• Presence of packaging material arising from poor or degraded container.	• The type found maybe a significant finding

Fungus-infected samples (especially with Aspergillus) are to be rejected outright because they may contain mycotoxins such as aflatoxins [18]

Table 7. List of tests relevant to herbal quality control and GMP

Name of test	Purpose of test
Macroscopic examination • Visual inspection: shape, size, color, texture, and appearance of cut surfaces • Organoleptic characteristics: odor and taste	Macroscopic examinations are for taxonomic authentication and characterization of plant materials based on visual inspection; and organoleptic characteristics
Microscopic examination – especially fresh sample Chemo-microscopic examination - fresh or dried	Useful for identification and characterization, and for detection of adulterants
Thin Layer Chromatography (TLC) • Simple TLC is a powerful technique • HPLC is High performance TLC	Useful for identification and characterization, and for detection of adulterants
Phytochemical tests • Major classes of phytochemicals • Specific phytochemicals (eg: cyanogenics)	Useful for characterization/ exclusion of unwanted phytochemicals
Hyphenated technique (eg: GC-MS)	Useful for detection/ quantification of constituents
Some physiochemical/ biophysical determinations ○ Loss of drying (LOD) ○ Total ash (TA) ○ Acid-insoluble ash (AIA) ○ Extractability in water (WEM)and other select solvents (SEM) ○ pH ○ Light absorption features ○ Others – especially intensely bitter and/ or foamy materials ▪ Bitterness value ▪ Foaming index	Useful as quality variables for GMP • LOD, useful for posology / GMP • TA is useful for GMP • AIA is useful for GMP • WEM or SEM is useful for posology and GMP • pH is useful for GMP • Light absorption, useful in GMP • Quality control variables (QCVs) such as bitterness and foaming indices are useful for GMP and for monitoring stability
Determination of select elements • Generally seen as useful (eg: K, Zn, and Se) • Generally seen as toxic (eg: Pb, Hg, and Cd)	Useful ness/ Reason for exclusion: • K, Zn, Se are useful as cofactors • Heavy metals, potentially toxic
Real time stability study of: • Herbal raw materials • Herbal finished products	In just the same as QCVs can be used to monitor GMP, they can be used to monitor stability or keeping quality

These tests are based mostly on WHO's prescriptions as contained in quality Control test for medicinal plant materials [18], as modified and described elsewhere [21,22]

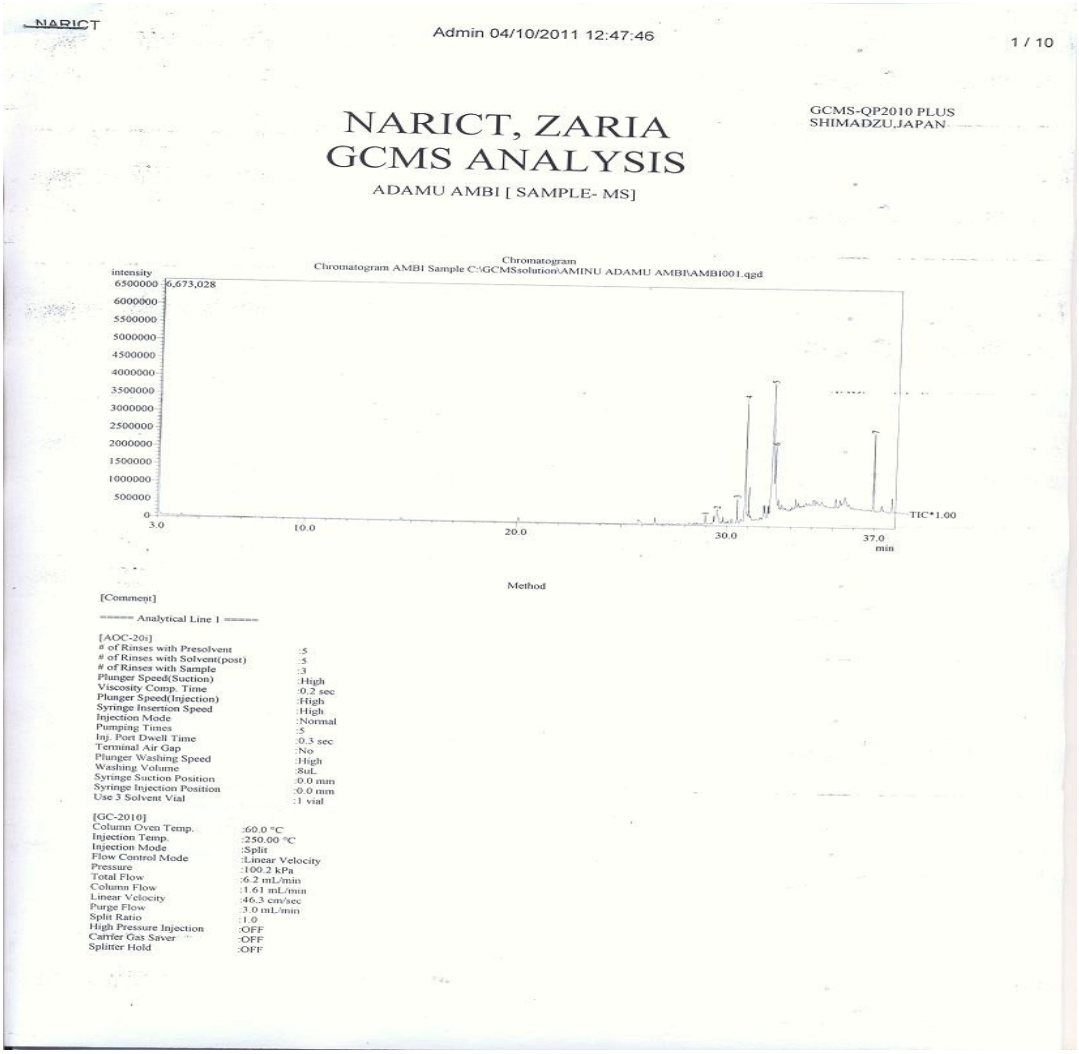


Fig. 2. GC-MS chromatogram of Niprifan

The chromatogram (abundance vs retention time) was generated with a Shimadzu GCMS-QP 2010 Plus. It shows 7 peaks corresponding Lines # 1 – 7 in the mass spectra. The sample was injected as 1µl of ethanolic solution containing 0.1µg of extract. Operational conditions were as indicated in the comment below the chromatogra[21,22]

10. PREPARATION OF DOSAGE FORMS BASED ON PHYSICOCHEMISTRY/ SELECT CONSTITUENT

10.1 Historical Progression of Dosage Forms

It is well documented that the use of herbal remedies has been on the increase since 1978, 1994, and 2004 [3,5,6]. Industrially produced or packaged remedies come in either of two forms:

- Fresh or dried whole herb or plant parts, eg: flowers, leaves, barks, roots, or rhizome [23,24]
- Standardized herbal extracts [23,24].

A whole herb (usually means aerial parts) or plant preparation may simply be:

- A fresh or dried plant part (usually consumed as is or decocted as a tisane.
- A dried and comminuted herbal material dispensed as a powder or granule that may be encapsulated or tableted.

A whole herb or select plant part contains all of the constituents of the whole plant or the select part. Such simple dosage forms were the precursors of modern dosage forms, and are as old as humankind. The data required for their production have been passed down through successive generations of herbalists. As earlier stated, the long histories of use of traditional herbal remedies generally bear testimonies of their safety and efficacy.

A standardized extract may be:

- An herbal material processed and preserved as a solution, emulsion, or suspension, in a suitable solvent such as an alcoholic beverage or edible oil.
- A standardized extract can also be supplied as dry powder, granules, capsules, or tablets.

Standardized extracts are relatively newer in the market and may be conceived to be more advanced than whole herb or select plant part preparations, but not necessary superior to the latter. The concept of standardized extract is briefly elaborated in a subsection below.

10.2 Variability of Contents of Herbal Dosage Forms

There is hardly any herbal material or dosage form that has only one indication. The main reason for this key fact is that every plant material contains scores of bioactives. Another is that: Though the chemical makeup of an herb can vary, it usually does so only slightly. This is because under a given set of conditions biological systems including plant parts maintain an equilibrium or homeostasis whereby the concentrations and ratios of metabolites are maintained within very narrow limits, depending upon effects of various of factors, including:

- Gender and genetic make-up of the plant or its population
- Age of the plant at harvest
- Soil type and environment in which the plant grows
- Part of plant harvested
- Time of day or season
- Method and time of harvest
- After-harvest processing technique

11. PREPARATION OF DOSAGE FORMS BASED ON ETHNOMEDICAL DATA/ EXTRACTABILITY

11.1 Illustration of Dosage Calculations using *Nauclea latifolia*/Niprd-AM1

When preparing a dosage form of *N. latifolia* (NL) based on ethnomedical data/extractability, the following steps are required, using powdered NL as the crude herbal drug (CHD):

11.1.1 Step 1

If the CHD is not in a form that can be readily weighed or measured out with a spoon, the quantity prescribed by the herbalist is first converted to powder. Powdered NL, whose physicochemical features are given in (Table 8) can be weighed or measured in heaps with a spoon.

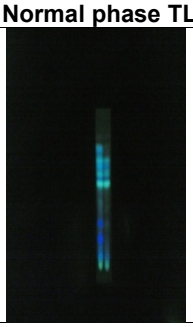
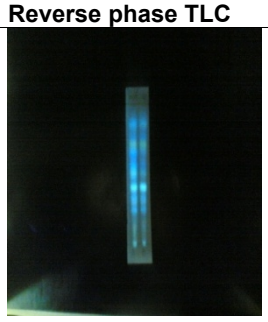
- Let the average weight of a heap of NL be 3.5g.

Table 8. Select physicochemical features of NL and Niprd-AM1

Characteristic	Raw Material (CHD) of NL				Aqueous Extract (ACE)			
Description of sample	Yellow, coarse or finely cut material; practically odorless. Powdered NL can be weighed or dispensed with a spoon				Yellow-brown granules; practically odorless or faint aroma			
					1st Day		14th Day	
Loss on Drying (LOD) %w/w	9.79±2.00 (30)				6.50±1.22 (8)		10.81±0.44 (7)	
Total Ash (TA) %w/w	3.09±1.28 (57)				9.88±2.60 (15)			
Acid insoluble ash (AIA) %w/w	Below detection				Below detection			
Water extractable matter (WEM) %w/w	16.56±3.93 (29)				-			
Wavelengths: (λ200-700nm) Solvent: water. Dilution: x 25 for herb mixture in water (1% w/v); x 125 for solution of extract in water (1%w/v). A1%1cm at λ225	Peak		Trough		Peak		Trough	
	λ	Abs	λ	Abs	λ	Abs	λ	Abs
	688	0.055	697	0.053	688	0.075	697	0.072
	454	0.090	548	0.048	454	0.120	548	0.053
	225	2.024	391	-0.087	225	2.224	391	-0.107
	253				278			

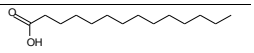
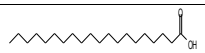
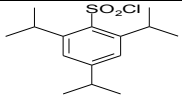
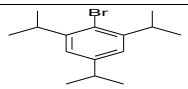
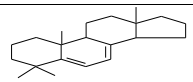
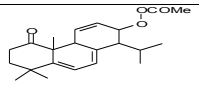
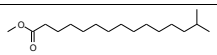
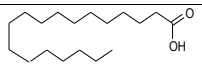
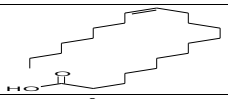
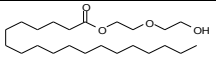
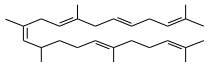
Samples of the ACE were prepared by hot extraction with boiling water. The results represent Mean ± SD. The following should be noted: The ACE is highly hygroscopic but not deliquescent. The TA of the ACE is about 3x that of the CHD, but acid insoluble matter was below detection, suggesting that the CHD is rich in bio-minerals, and that the TA of the ACE mainly contained physiological ash. The spectra revealed 3 peaks and 3 troughs. The absorption

Table 9. Phytochemical and TLC Profiles of NL and Niprd-AM1

Phytochemical constituent	NL	Niprd-AM1	Normal phase TLC	Reverse phase TLC
Saponins	+	+		
Terpenoids	+	+		
Alkaloids	+	+		
Flavonoids	+	+		
Cyanogenic glycoside	?	?	NL (L) and Niprd–AM1 (R) in ethanol developed with Hexane: Ethyl acetate (4:1) on K2 normal phase TLC, and viewed at 366 nm. NL yielded 9, while Niprd-AM1 yielded only 5 spots	NL (L) and Niprd–AM1 (R) in EtOH developed with Methanol: Water (4:1) on KC20 reverse phase TLC, and viewed at 366 nm. Both NL and the Niprd-AM1 yielded 9 spots.
Anthraquinones	?	?		
Cardiac glycosides	?	?		

(+): Indicates present. (?): Indicates absent or below detection[21,22]

Table 10. Summary of data from GC-MS chromatogram of Niprifan

Peak/ Line Number (#) as per GC/MS	RT (min)	Mass peaks	Base peak	Some likely compds. based on comparison with NIST05 LIBRARY	Corresponding structures
Peak/ Line #1	29.0	38	73	Tetradecanoic acid (Myristic acid) Mol Weight, 228	
				Eicosannoic acid (Arachidic acid) Mol Weight, 312	
Peak/ Line #2	29.5	56	187	Benzenesulfonylchloride-2,4,6-isopropyl, Mol Weight, 302	
				1-Bromo-2,4,6-triisopropylbenzene Mol weight, 282	
				4.4-Dimethyl Androsta-5,7-diene Mol Weight, 284	
				14-Isopropyl-1-oxopodoc (Phenanthrone derivative), Mol Wt, 342	
Peak/ Line #3	30.5	55	74	Methyl-14-methylpentadecanoate, Mol Wt, 270	
Peak/ Line #4	30.8	88	43	Octadecanoic acid Mol Weight, 284	
Peak/ Line #5	32.1	95	55	Erucic acid (Prifac 299) Mol Weight, 338,	
Peak/ Line #6	32.2	60	43	Clindrol SDG (Aqua Cera) Mol Weight, 372	
Peak/ Line #7	36.9	101	69	Squalene (Spenacene, Supraene) Mol Weight, 410	

The molecular entities above are constituents of MS or their intermediates or fragments. The high abundance of long aliphatic chains as in myristic and arachidic acids; and of lipids like phenanthrone, androstadiene and squalene, is consistent with the general hydrophobic nature of Niprifan. The benzene ring entities are evidently by-products of shikimic acid pathway via gallic acid - a known constituent of MS. Other C-H-O-entities are terpenoids like ursolic and oleanolic acids; and others like psoralen and tectoquinone, which are well known constituents of MS[21. 22]

Table 11. Effect of storage on the moisture contents of AP and Conavir

Months of storage in capped glass bottles at room temperature and humidity (RTH)	Loss on drying (mean ± SD) %w/w	
	Herb (AP)	Extract (Conavir)
0	9.84±0.66a (n=7)	10.07±1.90b (n=7)
3	8.64±0.59a (n=5)	10.84±1.03b (n=5)
9	9.14±0.66a (n=7)	12.14±2.33b (n=5)
21	10.77±0.86a (n=5)	9.84±2.06b (n=5)
39	8.96±0.46a (n=5)	11.44±2.03b (n=5)

The results show that the moisture contents of both the herb and extract did not change significantly (P > 0.05) as denoted by (a) for herb and (b) for the extract, during the storage period of 0 to 39 months. The results imply that changes in moisture content as a contributory factor to moisture induced instability or hydrolytic spoilage would be minimal[21,22]

Table 12. Effect of storage on light absorption and TLC characteristics on AP/Conavir

Months of storage in capped glass bottles at RTH	Herb (AP)			Extract (Conavir)		
	Absorbance at λ225 nm	TLC spots		Light absorption	TLC spots	
		NP	RP		NP	RP
0	0.083±0.015[a] (n=7)	5	6	0.291±0.037[b] (n=7)	5	6
3	0.107±0.025[a] (n=5)	5	6	0.306±0.031[b] (n=5)	5	6
9	0.115±0.025[a] (n=5)	5	6	0.292±0.031[b] (n=5)	5	6
21	0.078±0.015[a] (n=7)	5	6	0.240±0.031[b] (n=7)	5	6
39	0.091±0.015[a] (n=5)	5	6	0.276±0.031[b] (n=5)	5	6

Solutions of herb and extract were made by thoroughly mixing 1 part of solute and with 100 parts of solvent (MeOH: H_2O [52:48, v/v]), filtering, and diluting the filtrates by 150X with the same solvent. Absorbencies were measured at λ225 nm, using the solvent as the blank. Both ([a]) and ([b]) denote that any differences seen in the values were not significant (P >0.05). NP and RP mean normal phase and reverse phase respectively [21,22]

11.1.2 Step 2

If the dose of NL prescribed by the herbalist were as follows:

- Decoct 2 heaps with 1 “regular coke bottle” equivalent of boiling water (ie: 300ml).
- Allow the mixture to cool, and decant or filter the entire extract with filter
- Drink the entire extract in one draught

The above means that the dose of NL is: 7.0g

11.1.3 Step 3

(Alternative to step 2): If Niprd-AM1, the ACE of NL, whose features are also shown in (Table 8) were to be given, the quantity of 1 dose is calculated from the water extractive value of NL as follows:

- Water extractive value of NL is: 16.56%w/w (Table 8)
- From above 100 g NL is equivalent to: 16.56g of Niprd-AM1
- Hence 7 g of NL is equivalent to: 1.16g of Niprd-AM1

The foregoing calculation is based on air-dried samples, hence is necessary to know that "air-dried sample of NL" typically has an LOD value of 9.79%w/w, while that of Niprd-AM1 is 10.81 %w/w (Table 8).

11.4 Step 4

It is essential re-confirm that NL and Niprd-AM1 are what they are by ascertaining their phytochemical and TLC features given in (Table 9).

11.2 Use of GC-MS data illustrated with *Mitracarpus scaber*/Niprifan

Fig. 2 and Table 10 collectively represent GC-MS fingerprint of *Mitracarpus scaber*/ Niprifan, with some phytochemical details. Both can therefore be used for purposes of identification. A finer, more elaborate run/ study can be used to estimate amounts of stated constituents.

11.3 Use of storage data illustrated with *Andrographis paniculata*/Conavir

Table 11 shows the effects of storage on moisture contents of *Andrographis paniculata* (AP) as the crude herbal drug (CHD) and of Conavir as the active crude extract (ACE). Table 12 shows the effects of storage on light absorption and TLC features of AP and Conavir. The Tables collect demonstrated that changes in moisture contents as a contributory factor to moisture induced instability or hydrolytic spoilage are minimal and insignificant during storage from 0-39 months, as described previously [21,22]. Similarly, storage of samples from 0-39 months produced no significant effects of both light absorption and TLC features of AP and Conavir [21,22]. As will be demonstrated in a later section, storage data are essential for traditional-use registration as implied in Table 13.

12. THE CONCEPT OF STANDARDIZED EXTRACT

A standardized extract is an herbal extract that has been processed so that it contains a specified amount of a certain component, usually the one thought to be the active ingredient. The amount is then stated on label to inform consumers that the product in question contains the stated amounts of that component [23,24]. Thus, a standardized herbal extract is one that has one or more components present in a specific, guaranteed amount, usually expressed as a percentage (% w/w, w/v, or v/v). The intention behind the standardization of a botanical is to guarantee that the consumer is getting a product in which the chemistry is consistent from batch to batch [24]. This practice evolved from the pharmacological model of herbal action, whereby chemistry and biomedical science attempt to identify and attribute to specific plant constituents as being responsible for a given pharmacological activity.

13. DRAWBACKS OF STANDARDIZED EXTRACTS

Although modern chemistry enables isolation of many constituents from a plant; and biochemistry and molecular pharmacology can discover how particular phytochemicals may act in the body, the fact is that these sciences inadvertently remove or overlook constituents that may contribute to the activity of the whole plant, or parts. The implications are as follows:

- Extract standardization may concentrate one constituent at the expense of other potentially important constituents
- Extract standardization may change the natural balance of a given plant constituents, which may result in loss of activity.

14. A MODIFIED PHARMACOLOGICAL MODEL OF HERBAL ACTION

It seems evident from the foregoing that: “The full medicinal value of herbs is most likely due to their internal complexity and to the interactions of the different components within the body rather than to one of its specific components” [24]. Moreover, there are still many unidentified plant constituents, whose properties and spectrum of interactions are unexplored. Plants still hold many secrets, for example: It was only recently discovered that “Tramadol – a synthetic drug is one of the components of *Nauclea latifolia* [25] It is noteworthy therefore, that *Nauclea latifolia* is the plant of Niprd-AM1 [21,22].

15. USE OF MARKER SUBSTANCES IN HERBOLOGICAL STUDIES

Aside from the use of a putative active constituent in standardized extracts, another form of standardization uses a key but supposedly a “non-active constituent” only as a marker of identity (or quantitative presence) rather than of activity, in the bid to study herbal distribution or kinetics. Such standardized extracts may or may not fulfill the purpose of such a study however, because such a marker substance may not have a similar pattern of distribution as the putative active constituents. But, if the marker is the active constituent or similar to it, its use in such a study might be informative, especially if that marker is easily detectable and quantifiable. That is to say, the use of such a marker may guarantee that the “herbal substance in its entirety” will have a minimum level of potency all the time without sacrificing any constituents, once the marker is seen to uniformly distributed, or can be detected in the tissues of interest. This explains why in herbalism each herbal substance or material in its entirety is regarded as a drug [16,26]. For example, the label of Niprisan would simply state that each 250mg capsule contains: *Piper guineense* (a mg); *Eugenia caryophyllata* (b mg); *Pterocarpus osun* (c mg); *Sorghum bicolor* (d mg); trona (e mg); and excipients (qs). This is despite the fact that each herbal component is made of many constituents [13,26].

Furthermore, not all manufacturers standardize their products to the same constituents. In addition, it is known that some producers “standardize” to more than one phytochemical constituent. For example, St. John's Wort preparations used to be standardized to contain 0.3%w/w of hypericin, but of late, some producers have, in addition to hypericin, included hyperforin (2-5%w/w) in their brands of St. John's Wort. Hyperforin is another natural constituent of *Hypericum perforatum* [23,24].

16. TRADITIONAL-USE REGISTRATION IN EU AND NIGERIA COMPARED

16.1 Requirements for Herbal Drug Registration in Europe and Nigeria

The requirements of EMEA and NAFDAC for herbal drug registration are summarized in (Table 13). These requirements featured in planning the studies described in detail elsewhere [21,22] and in preparing this review article. The requirements are described under the following subheads:

16.2 Product Information/Legal Status of Applicant

Both EMEA and NAFDAC require product information but EMEA was more explicit in its requirements for technical data on “product characteristics” than was NAFDAC, which harped more on the “legal status of the applicant”, rather technical detail of product [27-29].

16.3 Quality Control Data/Analytical Status of the Product for Registration

EMEA requirements were more comprehensive and explicit and were hinged on “GMP compliance”. By contrast NAFDAC requirements were less explicit but touched on all key issues pertaining to GMP. NAFDAC harped “analysis certificate” But mere presentation of analysis certificate for a product is not enough, unless both the analyst and the methods used are appropriately authorized.

16.4 Safety Data Requirements/ Pre-Registration Inspection of Premises

Both EMEA and NAFDAC addressed safety [27,28]. EMEA was however far more detailed on safe use of the product, while NAFDAC was more concerned with the storage, distribution and integrity of the product, which though important, are secondary issues. Moreover, unlike EMEA which made no reference to money, NAFDAC informed prospective applicants [29]: read as follows:

“HOW MUCH DOES IT TAKE TO CONDUCT CLINICAL TRIAL IN NIGERIA?

- The applicant needs to pay NAFDAC N200000 plus 5% VAT for imported products and N50, 000.00 plus 5%VAT for local and herbal products.
- Other monetary expenses related to the conduct of the trial are handled between the sponsors and the investigators” [29].

A pertinent question is: Should NAFDAC conduct, or supervise clinical trials? Given the high cost of even the cheapest clinical trial, one must assume that the “N50000”or “200000” for herbal “clinical trials” only covers NAFDAC’s admin charges. If NAFDAC fees alone amount to“N50000”or “200000”, how much would the applicant pay the “consultants” that will conduct the “clinical trial”? Who recommends, approves or regulates a “clinical trial consultant”? Is there a register of such consultants and their track records? Can NAFDAC satisfactorily answer these questions? If it cannot, and given the rampancy “sharp practices in product regulations” especially in developing economies like Nigeria, the following can be surmised: It is precisely for the avoidance of “sharp practicesthat traditional-use registration comes into play. The average Nigerian herbalist is unlikely operate at an annual turnover of up to N10000, so N50000 is a lot. NAFDAC’s scheme for “listing” is unlike to attract the warm accolade showered on the EU Parliament by Ayurvedic herbalists in Europe and India, when the EU’s Directive on traditional use registration became public [30].

Table 13. Requirements for traditional-use registration of TM products EU and Nigeria

European union (EU)		Nigeria	
Type of data	**Details of data required**	**Regulatory aspect**	**Requirement**
Product information: Summary of product characteristics	These include: name, strength, dosage form, list of excipients, shelf life, posology, indications, contraindications, and special precautions. These are used as basis for inserts or advertisement, which must undergo a process called “readability”.	Legal status of applicant - manufacturer or marketer	Applicant must be certified by the Corporate Affairs Commission as a business. A marketer must show evidence of Power of Attorney.
Quality control data: Refer to GMP requirements for production.	These include: production must be in a GMP compliant, product must be produced with validated formula and method, there must be a product specification, stability studies must be carried out in the container proposed for marketing for purposes of storage/ shelf-life, and dossiers must be provided for starting materials and finished product.	Analytical status of the product for registration.	The product must have: certificate of analysis, dossier containing data on ingredients, method of analysis, stability, dosage and safety precautions.
Safety data requirements	The data may be assembled from: animal or human studies, review of potential drug-drug interactions, side effects and contraindications. Others include: recognized monographs, data special groups - children, the elderly and mothers.	Pre-registration inspection of premises.	Manufacturing, storage and distribution premises must be GxP compliant. Marketers must provide convincing evidence of GXP
Traditional use evidence	Evidence that the product has been in use as medicine for 30 years or more (the last 15 must be in the EU. Notably, there is no requirement to prove efficacy [32].	Post marketing surveillance plan/ report	Applicant may be required to provide a plan for reporting on the use of the product and of any adverse reactions.

The Table is based largely on various NAFDAC leaflets, including Akunyili [28] and NAFDAC website: www.nafdac.org; and on De-Smet [32] Ann Godsell Regulatory [33]. By contrast with EMEA [1,27] which is detailed and helpful to applicants, the scantiness of NAFDAC’s scheme for “listing” makes it practically unusable for the intended purpose

Once money inappropriate occupies the center stage in any regulatory activity corruption is never far away. Indeed, in 2000, NAFDAC's entire management was sacked by the 1st democratically elected President since 1983, on alleged corruption. In 2007 the Head of China's DRA was sentenced to death for corruption [31]. These explain why better funding mechanisms, policies and legislations, transparency and vigilance are required for proper DRA functioning.

16.4 Traditional Use Evidence/ Post-marketing Surveillance

While EMEA and the EU Directive stressed the importance of traditional use evidence, NAFDAC overlooked it altogether, but discussed post-marketing surveillance, which, though important, is secondary. Even the words and tone of NAFDAC's information [29] to prospective herbalists are in marked contrast to those EMEA and the EU Directive [1,27-29].

17. CONCLUSION

1. The approach described in this article can be used to get more TM products registered by drug regulatory agencies (DRAs). But, there is a need, especially in emerging polities, for Research Institutes/ Universities to team up with their national DRAs, to work out and agree the following:

    - A list of requirements for traditional-use registration of herbal remedies
    - A system of coordinated herbaria and reference herbal substances
    - A system of committees on traditional-use registration, with members drawn from interested parties, including herbalist and industrialists.

2. The foregoing collaborations/ systems will facilitate and encourage more effective utilization of traditional knowledge and resources.
3. The same collaborations/ systems will facilitate the passage of more effective laws.
4. Moreover, as described elsewhere [34-37], there is a great need for DRAs and Research Institutions/ Universities in developing polities like Nigeria to be self-regulating by embracing appropriate quality management system (QMS) practices such as ISO 9001 for whole institutions like NAFDAC and NIPRD, and ISO/ IEC 17250 for their laboratories.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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