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Systematic organization of medicinal plant information: a monograph template proposal

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ABSTRACT

The use of medicinal plants in Brazil is widespread and is supported by public policies; it has the objective of providing the population with safe and effective herbal medicines of adequate quality. An action in these policies is to develop medicinal plant monographs to gather published information and decide which medicinal plants should be financed by the Brazilian government and distributed by the public health system. Currently, the monographs published worldwide do not present unified information regarding medicinal plants, and generally, they do not cover enough requirements for herbal medicine registration. The aim of this study is to develop a monograph model with standardized information not only about botany, agronomy, quality control, safety, and efficacy but also about relating regulatory aspects that support herbal medicine regulation. The development of standardized monographs favors the fast authorization and distribution of herbal medicines in the public system. The model also points out the lacking studies that should be carried out to supplement the necessary regulatory information of medicinal plants.

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Introduction

Brazil is one of the countries with the largest biodiversity of the world; however, most of it remains unexploited (Gonçalves et al., 2010). Brazil is also considered to house a large number of researchers. Nevertheless, knowledge generated by these studies is generally not applied for launching new products to the market, resulting in few herbal medicines made of Brazilian medicinal plants (Carvalho et al., 2008; SBPC, 2005).

In 2006, the Brazilian government published the National Policy of Integrative and Complementary Therapies, which includes phytotherapy in the public health system (*Sistema Único de Saúde*, SUS) (MS, 2006). In addition, in 2006, the National Policy of Medicinal Plants and Herbal medicines was published establishing the major actions to ensure the rational use of herbal medicines according to national legislation and international recommendations (Brasil, 2006).

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In 2009, the Brazilian Ministry of Health published the List of medicinal plants of interest for SUS (Renisus), which included those considered as potentially valuable for the generation of herbal medicines. Researchers have been encouraged to make use of this list as a guide to select species to study. The resulting information regarding the species can then be used to prepare the national lists of herbal medicines and medicinal plants, and promote development and innovation in the field of medicinal plants (MS, 2009).

Several monographs have been published worldwide, some of which are used as sources of information by many countries, such as the WHO Monographs on Selected Medicinal Plants (Veiga Junior and Mello, 2008; WHO, 1999, 2003, 2004, 2007, 2009)

The two kinds of official monographs in Brazil are the Brazilian Pharmacopoeia, which includes quality control tests for synthetics and herbal medicines, and the *Formulário de Fitoterápicos da Farmacopeia Brasileira*, which includes safety of herbal formulations for pharmaceutical compounding. Along with these official Brazilian references, some selected foreign pharmacopoeias are officially used in Brazil, such as the United States Pharmacopoeia (USP) and USP National Formulary, the International Pharmacopoeia (from the World Health Organization - WHO), and Germanic, Argentinean, British, European, French, Japanese, Mexican and Portuguese pharmacopoeias (Anvisa, 2009b), as well as other unofficial monographs: *Monografias de plantas medicinais brasileiras e aclimatadas* (Gilbert et al., 2005); *Farmácias Vivas* (Matos, 2000), and books including monographs of medicinal plants published for Brazilian phytotherapy public services. Scientific journals and articles are used also to gather information about medicinal plants. However, usually, each monograph or paper presents different approaches and do not face all the important requirements needed for a thorough documentation about medicinal plants, such as botanical authentication, cultivation, quality criteria, safety, efficacy, market, and regulatory issues (Veiga Junior and Mello, 2008).

Thus, a monograph template, including mandatory aspects as determined by Anvisa (Agência Nacional de Vigilância Sanitária) as well as international regulations, was developed. The objective is to systematize the available information on medicinal plants of interest to the Brazilian public health system.

The monograph template includes information considered relevant for the use of medicinal plants, based on a review of the scientific literature and databases to compile all previously published information on specific medicinal plants. This model's intent is to allow for remaining non-fulfilled items in the monograph be used to guide future research and financing by the Brazilian government.

Thus, after fulfilling this model with pre-published data on the plant species included in the Renisus (Relação Nacional de Plantas Medicinais de Interesse ao SUS), it will be possible to identify which are the more studied medicinal plants having sufficient data on their safety and efficacy, to be subsequently financed by SUS, and gradually included in the list of herbal medicines with simplified registration by Anvisa (2008a). The products included in this list must follow a strict set of standardization so the registration process is easier and faster

than usual registration. For the less studied medicinal plants it would be possible to indicate which studies are needed to validate its use.

The monograph template presented herein is intended to be used by researchers funded by the Brazilian Ministry of Health to evaluate the plant species included in the Renisus. Following their completion, monographs will be reviewed by experts in the areas of interest and will be initially published as a public consultation to allow all stakeholders to contribute to the final monograph. It is also envisaged that the monograph template will guide the research and inclusion of important information for the publication of medicinal plant data. Thus, articles and books published under this model may be quickly recognized by Anvisa, among their reference lists, for evidence of safety, efficacy, and quality of herbal medicines.

Material and methods

Building the template

To support the template proposal, a comparative and exploratory study was performed by a comparison and consideration of the set of information presented in the monographs listed by Anvisa Normative Instruction 05/10 (Anvisa, 2010e): WHO Monographs on selected medicinal plants, tomes 1-4 (WHO, 1999, 2004, 2007, 2009); European scientific cooperative on phytotherapy - Monographs on the medicinal uses of plant drugs (ESCOMP, 1996); American Herbal Pharmacopoeia (Upton and Petrone, 1999); *Monografias de plantas medicinais brasileiras e aclimatadas* (Gilbert et al., 2005), British Herbal Compendium (Bradley, 2006); Expanded Commission E monographs (Blumenthal, 1999; Blumenthal et al., 2000); and *Vademécum nacional de plantas medicinales* (Cáceres, 2006). This data is available at Carvalho, 2011.

The next step was the evaluation of regulation requirements for herbal medicine registration and for plant notification at Anvisa, as well as requirements on regulations for herbal medicines from other agencies such as: European Medicines Agency (EMA), Health Canada (HC-SC), *Comisión Federal para la Protección contra Riesgos Sanitarios* (Cofepris), *Administración Nacional de Medicamentos, Alimentos y Tecnología Médica* (ANMAT), and the Paraguayan Health Ministry (Anmat, 1998, 1999a, b; Cofepris, 1998a, b, 2000, 2001, 2006, 2013; EMA, 2006a, b, c, d, 2007, 2008a, b, 2010a, b, c, d; HC-SC, 2003, 2006, 2007, 2010a, b; Paraguai, 1997). A preliminary template was created to verify if all the requirements were present, after which the template was submitted to peer review evaluation of the members of the Anvisa Herbal Medicine Technical Chamber (CATEF) and the Support Committee of Medicinal Plants and Herbal Medicines Policy from Brazilian Pharmacopoeia (CTT-APF) (Anvisa, 2010b; CATEF, 2010). The new template, with the reviewer-suggested modifications included, was tested at the preparation of the *Maytenus officinalis* Mabb., Celastraceae, monograph (unpublished results).

Results and discussion

The template

The proposed template is divided into seven main sections, namely: general information, pharmacognostic authentication, agronomical information, quality control, safety and efficacy, other information and references.

General information

This section must include all accepted names and basic information about the plant species, including vernacular name, scientific name, all known synonyms, images, and geographic distribution. Geographic distribution is important considering eventual financial support because Brazilian native species should be prioritized (Brasil, 2006).

Several useful free databases, such as “The plant list” and *Lista de espécies Flora do Brasil* can be accessed to ensure accuracy of the information. *Lista de espécies Flora do Brasil* database includes information on over 40,000 Brazilian species (JBRJ, 2012; MBG, 2013).

Pharmacognostic authentication

This section refers to plant parts or organs used as raw materials in herbal medicine production and should be as complete as possible to allow correct species identification. This information is usually found in pharmacopoeias. In Addition, *Brazilian Pharmacopoeia* presents figures showing the macro and microscopic characteristics from particularly useful herbal drugs (Anvisa, 2010a; Veiga Junior and Mello, 2008). Furthermore, this section should present information about all known species that could be used for counterfeit or misidentification, an important point for quality control. Data on other species used in folk medicine misidentified as the same plant or vernacularly named as the described plant species should be informed, particularly for native species. This information is valuable considering that in Brazil it is not rare that different species share the same vernacular name. Nevertheless, according to Brazilian regulation, to register a herbal medicine a complete dossier for the specific medicinal plant is mandatory, and all others species not presented at the dossier are considered as contamination (Anvisa, 2010a, b; Veiga Junior and Mello, 2008).

It is important to check for already collected and published data, which should also follow best practices, in this case, related to Botany. There are recommendations for collecting and cataloguing specimens, in relation to sustainability issues, as there are particular specifications for collecting, drying, and preparing of herbarium specimens (WHO/IUCN/WWF, 1993). Thus, if there is documentation regarding gathering and recording of vouchers specimens, this information should be included in the monograph.

Agronomical information

This section aids the implementation of the Good Agricultural Practices the first step in herbal medicine manufacture. This section should include data concerning the biology, phenology,

production system, cultivation method, processing, storage, and seed characteristics (Scheffer et al., 2006).

Furthermore, this section's data can help define strategies to improve the culture of target species to achieve better yields of selected phytopharmaceuticals. Agricultural practices can directly affect the quality of herbal medicines. International guidelines (e.g. WHO) can be used, given the lack of specific regulations in Brazil (Scheffer et al., 2006; WHO, 2003).

Agronomical information in this section enables the collection of data to assist projects for the standardized, homogeneous, and continuous production of plant materials; as well as the reproduction and genetic preservation of species of interest and biodiversity conservation. Information on the influence of seasonality over raw material productivity, active compound yield, and toxicity is important, as well as phytosociology, ecology, successional groups, and threat of extinction should be included.

Other crucial activities that should be controlled, such as soil analysis, pesticide contamination control, and water quality for irrigation to avoid plant drug pollution, should be described. Crop techniques and phytosanitary issues determine plant development and, consequently, the productivity and active compound yield (Scheffer et al., 2006; WHO, 2003). Much standardized agronomy information may not have yet been established for the medicinal plant described at the monograph, particularly when the plant is obtained by extractivism (wildcrafting). Thus, the item must be completed with the information “the requested data has not yet been published”.

Quality control

Concerning Brazilian regulation, the requirements for the quality control of herbal medicines are defined by RDC 14/10 (Anvisa, 2010e), and those related to pharmaceutical stability and analytical method validation are defined by RE 01/05 and 899/03 (Anvisa, 2003, 2005). For notifiable plants (herbal drugs traditionally chosen for simplified sales authorization), the quality control requirements are specified by RDC 10/10 (Anvisa, 2010c).

For herbal medicines, controls should be performed at all production steps, including the raw materials, which may be herbal drugs or herbal preparations, and the final product, the herbal medicine. All available published information on these tests and specifications standardized for the medicinal plant must be included in the monograph.

For the herbal drug, information about specifications on granulometry/particle size, organoleptic properties, presence of foreign materials such as ash, moisture, microscopic and macroscopic contaminants including fungi, bacteria, mycotoxins and heavy metals, should be given. Finally, qualitative and quantitative markers should be listed (Anvisa, 2010b).

For the herbal preparation, the extraction methods and the possibility of residual solvent presence must be included. For the final product, the control varies according to the dosage form, but it must guarantee the integrity and stability of the product, as well as the control level of microbial contamination (Anvisa, 2010d). Possible contaminants and the tests for identification and quantification of markers should be included

in the following three stages: herbal drug, herbal preparation, and the herbal medicine itself (Anvisa, 2010e).

In general, the official pharmacopoeias must be used to complete this section. The Brazilian Pharmacopoeia, 5th Ed. presents sixty monographs on medicinal plants and plant preparations. From these, only twelve refer to medicinal plants listed by Renisus. In the General Procedures section or in specific plant monographs of Brazilian Pharmacopoeia, protocols can be found for identification, microbiological control, ash content, humidity, and marker compound limits (Anvisa, 2010a).

Brazilian legislation prohibits the use of pesticides in medicinal plant crops. However, as this practice is allowed in several countries, and considering that Brazilian pharmaceutical companies can import the herbal raw materials, the presence of these substances must be stated. Therefore, all available information on pesticide limits for the medicinal plant should be included.

Any data available in the scientific literature regarding the best analytical techniques and specifications applied to each species, such as the use of thin-layer chromatography or high performance liquid chromatography for identification tests, should be stated.

Safety and efficacy

To register herbal medicines in Brazil, as done by the European community, pharmaceutical companies may present data on traditional use or non-clinical and clinical studies.

Information about traditional use

This section of the monograph should include information on the traditional use of the plant species, which, according to Brazilian law, must be demonstrated for a period of at least 20 years (long-term safe use), without serious adverse reports. Also, it should include studies demonstrating that the medicinal plant or herbal medicine does not contain toxic constituents.

Information about nonclinical and clinical assays

In agreement to Brazilian legislation, if there is not enough data on the traditional use of the medicinal plant, it is necessary to present data on non-clinical and clinical studies, which can be previously published. Only if enough data is not available, it will need to be tested by the company that intends to register the product. Considering this information, this section should include data on pharmacological and toxicological assays, separated by non-clinical and clinical studies (Anvisa, 2004, 2008b, 2010e; CNS, 1996, 1997). This structure was designed to present a panoramic view of the species and its derivatives, enabling detection of the most studied derivatives. However, many of the plants do not have complete clinical study data; subsequently, after reviewing the published literature and completing the monograph, it will be easy to find which species studies still require research and, thus, financing.

Data should be organized in a systematic way, such as by part of plant, derivative, chemical composition of the extract, tested doses, methodology, models, results, and references.

Non-clinical toxicology data should be divided into acute toxicity, sub-chronic, and chronic tests. According to Brazilian

RE 90/04, information regarding mutagenicity, genotoxicity, dermic sensibility, and cutaneous and ocular irritation should also be informed (Anvisa, 2004).

In accordance to RDC 47/09 or RDC 10/10, this section should also include information regarding route of administration, daily doses, posology, adverse effects, contraindications, risk groups, time limits for usage, precautions, interactions, and overdose effects (Anvisa, 2009a, 2010c).

Other information

Finally, the proposed template also presents a section on pharmaceutical form and formulation. Patent information can easily be found online at webpages such as *Instituto Nacional de Propriedade Industrial*, World International Property Organization, European Patent Office and Japan Patent Information Organization (EPO, 2011; INPI, 2011; JAPIO, 2011; WIPO, 2011). This information is important for the Ministry of Health, since it is preferable to finance research on non-patented extracts that can be produced at more affordable prices.

Other information should be included, if available in the scientific literature, such as special packaging, labeling, storage, and transportation (*e.g.*, if the product must be protected from light). In addition, all known official or unofficial published monographs worldwide on the specific medicinal plant, including data regarding quality control, safety, and efficacy must be stated. Information about the regulatory conditions in other countries and licensing by Anvisa and/or other regulatory agencies, as obtained through official reports or publications, is also required. This information is important because this data shows that the medicinal plant has been evaluated and that its use in other countries was allowed, helping confirm its safety and effectiveness. Regulations of ANMAT, EMA, and HC-SC usually consider an existent herbal medicine register as a positive item in the registration process.

In Brazil, the extensive number of product registrations for the same species will favor its inclusion among those financed by SUS.

References

This section presents a Chart containing all scientific references used to elaborate the monograph on the medicinal plant used, including the category of the information (Pharmacology, Agronomy etc.).

The suggested referencing style is Vancouver. The scientific information required to complete the monograph can be found at PubMed, Lilacs, Napralert, Science Direct, CAPES thesis, Scifinder, Micromedex, Scopus, Biological Abstracts, Medscape, Toxnet, and other databases.

Conclusions

A review of published studies/information on each medicinal plant of interest to the Brazilian government according to the developed template should provide complete information on each medicinal plant. Information obtained in the monograph will help for the evaluation of available information on a specific plant species and the

necessary effort to complete any missing information. Such evaluation is important in the decision-making process for the funding of further studies on the quality, efficacy, and safety of medicinal plants. The scientific data on the monograph must be constantly re-evaluated and the monograph needs to be re-published, so that the new information available in the scientific literature can be updated. The suggested period for review of each monograph is each year, based on our experience with *M. ilicifolia* monograph (unpublished data): an evaluation showed that one year after the elaboration of the monograph, several scientific studies had already been published.

Authors' contributions

ACBC (PhD student) contributed in data collection about herbal medicines legislation and elaboration of the monograph template. LAS revised the international monographs and the monograph template. DS contributed to critical reading of the manuscript and supervised the elaboration of the monograph template. All the authors have read the final manuscript and approved the submission.

Conflicts of interest

The authors declare no conflicts of interest.

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Monograph template:

1. General information

- 1.1. Latin name
- 1.2. Synonyms
- 1.3. Family
- 1.4. Image of the plant
- 1.5. Popular names
- 1.6. Geographical distribution

2. Botanical authentication

- 2.1. Part used/organ types
- 2.2. Macroscopic description
- 2.3. Microscopic description
- 2.4. Information on similar plant species that can be used as adulterants
- 2.5. Information on voucher specimens

3. Agronomic information

- 3.1. Biology and phenology
 - 3.1.1. Sexual system
 - 3.1.2. Flowering time
 - 3.1.3. Fruiting period
- 3.2. Form of fruit and seed dispersal
- 3.3. Production system
 - 3.3.1. Information on seeds
 - 3.3.2. Harvesting and processing
 - 3.3.3. Seed weight (by mg/1,000 seeds)
 - 3.3.4. Productivity
 - 3.3.5. Dormancy of seeds
 - 3.3.6. Longevity and storage
- 3.4. Germination
 - 3.4.1. Information on crop
 - 3.4.2. Description
 - 3.4.3. Propagation
 - 3.4.4. Growth and production
 - 3.4.5. Characteristics of the soil
 - 3.4.6. Climatic characteristics
 - 3.4.7. Time of collection/harvesting
 - 3.4.8. Habit and regeneration
 - 3.4.9. Consortium
 - 3.4.10. Agroforestry system
 - 3.4.11. Breeding
 - 3.4.12. Pests and diseases (occurrence, level of damage and control)
- 3.5. Processing information
 - 3.5.1. Drying
 - 3.5.2. Processing
 - 3.5.3. Expected return
 - 3.5.4. Packing
- 3.6. Storage information
- 3.7. Information on seasonal variation of markers
- 3.8. Information about whether the management affects markers
- 3.9. Ecological aspects

4. Quality control information (to be completed for plant species, plant preparations, and the final product - the herbal medicine).

Chart 1: Information about quality control

Herbal drug	Herbal preparation	Herbal medicine
Granulometry/ particle size	Description	Dosage forms
-	Methods of production	Specific tests for each pharmaceutical form
-	Physicochemical tests	-
Organoleptic characteristics		-
Purity requirements		
	Microbiological testes	
	Humidity	
	Heavy metals	
	Chemical residues	
	Ashes	
Phytochemical analysis		
Identification test		
Quantification tests (Chemical constituents and concentrations):		
	Described	
	Markers or active compounds	
Other considerations related to quality control		

5. Safety and efficacy information

- 5.1. Information on traditional use
- 5.2. Information about nonclinical and clinical assays
 - 5.2.1. Nonclinical toxicology
 - 5.2.1.1. Subchronic
 - 5.2.1.2. Chronic
 - 5.2.1.3. Genotoxicity
 - 5.2.1.4. Dermic sensibilization
 - 5.2.1.5. Cutaneous irritancy
 - 5.2.1.6. Ophthalmic irritancy
 - 5.2.2. Nonclinical pharmacology
 - 5.2.2.1. Nonclinical pharmacological assays
 - 5.2.3. Clinical trials
 - 5.2.3.1. Phase I
 - 5.2.3.2. Phase II, including pharmacokinetics and pharmacodynamics
 - 5.2.3.3. Phase III
 - 5.2.3.4. Phase IV
- 5.3. Summary of actions and indications for drugs derivatives
- 5.4. Routes of administration
- 5.5. Daily dose
- 5.6. Posology
- 5.7. Period of use
- 5.8. Contraindications
- 5.9. Risk groups
- 5.10. Warnings
- 5.11. Adverse effects
- 5.12. Drug interactions
 - 5.12.1. Described
 - 5.12.2. Potential
- 5.13. Overdose information
 - 5.13.1. Description of the clinical situation
 - 5.13.2. Actions to be taken

6. Other information

- 6.1. Dosage forms/formulations described in the literature
- 6.2. Products registered at Anvisa and other regulatory agencies
- 6.3. Packaging and labeling information
- 6.4. Monographs about the medicinal plant in oficial and unofficial compendia/codex
- 6.5. Patents applied for the plant species
- 6.6. Curiosities

7. List of references**Chart 2: References**

No	Author and title	Year	Knowledge area	Reference
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