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Selecting Medicinal Plants for Development of Phytomedicine and Use in Primary Health Care

Wagner Luiz Ramos Barbosa[1] et al.*
[1]*Universidade Federal do Pará*
Brazil

1. Introduction

The world market for herbal medicines is around US$ 40 billion, whereas in Brazil it is estimated to be around US$ 1 billion. Data from the World Health Organization (WHO) shows that more than a half of the world population makes use of some type of medicinal herb searching for relief for painful or unpleasant symptoms. From that total at least 30% are provided by medical prescription (WHO, 1978).

The application of traditional or popular knowledge about the use of healing plants, in the development of herbal drugs proves to be a fairly consequent and consistent strategy, as it can generate employment and income from the participation of the organized community in the process of development, production and insertion of the so developed product in the pharmaceutical market. It still may be appropriate from an ecological standpoint, when the botanical raw material for the production of this herbal medicine is obtained from specimens grown in deforested areas. When a project with this design is originated and developed in the scope of Pharmaceutical Sciences it is called an Ethnopharmaceutical study (BARBOSA, 1998).

Since 2006, the Popular Phytotherapy became a therapeutical option supported by the Brazilian government, through the National Policy on Integrative and Complementary Practices (BRAZIL, 2006). After that, new regulatory documents have been promulgated to standardize the use of medicinal herbs. The National Policy on Phytopharmaceuticals and Medicinal Plants in its guidelines, establishes that a list of regional plants is to be defined, representing the Regional Popular Phytotherapy (BRAZIL, 2006b). These policies advocate the inclusion of the use of medicinal plants in primary health care, which shall be employed with highest efficacy and safety and must be object of the actions of Pharmaceutical Services, which are also to be applied to manufactured drugs (BARBOSA & PINTO, 2005).

* Myrth Soares do Nascimento[1], Lucianna do Nascimento Pinto[1], Fernando Luiz Costa Maia[1], Antonio Jorge Ataíde Sousa[1], José Otávio Carréra Silva Júnior[1], Maurícia Melo Monteiro[2] and Danilo Ribeiro de Oliveira[3]
[2]*Universidade do Estado do Pará, Brazil*
[3]*Universidade Federal do Rio de Janeiro, Brazil*

The National Policy on Phytopharmaceuticals and Medicinal Plants (BRAZIL, 2006b) has the overall objective "to ensure the Brazilian population the safe access and rational use of medicinal plants and herbal medicines." The Pharmaceutical Sciences can contribute strongly to this purpose, attending the first specific objective of the document, "expand the therapeutic options for users with guaranteed access to medicinal plants, herbal medicines and services related to herbal medicine, with safety, efficacy and quality regarding the integrality of health care, considering the traditional knowledge about medicinal plants." Achieving this goal requires the combination of elements of Pharmaceutical Sciences such as Pharmaceutical Care and Quality Control, with traditional knowledge.

This concern of the regulatory agency promotes the standardization of herbal medicines facilitates the evaluation of important aspects such as efficacy and safety in the use of these medications, as the difficulties to standardize the active pharmaceutical ingredient and the formulation development of phytomedicines from medicinal plants of popular use represent the major challenge in the country.

Phytomedicines must contain as active ingredients exclusively plant material derivatives. The addition of an isolated substance from any source eliminates this characteristic of the product. Apart from the methodology chosen for processing the plant material, one must consider the seasonality of its biochemistry, the soil and climate characteristics of its growing place or occurrence and the popular and scientific names of the plant (MACIEL, 2002). Studies show that the secondary metabolism of the plant can vary considerably depending on factors such as: seasonality, temperature, water availability, UV radiation, nutrients, altitude, air pollution, and even induction by mechanic stimuli or attack by pathogens (GOBBO-NETO, 2007). Thus, for developing a phytomedicine it is determining to have a well defined plant species, including the unambiguous botanical characterization.

How to define from which plant species an herbaceous medicine can be developed?

There are some strategies to reach this definition and here we will discuss about some of them which are well known and a new one will be introduced, where therapeutic products are directly handled, and which was born within the Pharmaceutical Science.

The WHO has recommended that member countries, especially the developing ones, shall seek to expand their therapeutic arsenal for public health through the use of medical home practices employed by the people. These recommendations are summarized in the four items mentioned below (MATOS, 2000):

- Undertake regional surveys of plants used in the practice of people's or traditional medicine and scientifically identify them;
- Support the use of useful practices selected by their efficacy and safety;
- Suppress the use of practices considered useless or harmful;
- Develop governmental programs that allow the cultivation and use of the selected plants.

The scientific research on medicinal plants generally originates medicines in shoter time, often with lower costs and therefore more accessible to the population, which in different places on the planet, can't afford the high costs of medicines used to face the primary needs in health care, especially because in most cases the raw materials used in manufacturing these products are imported. For these reasons or deficiency of the public primary health care in Brazil, about 80% of the population lacks access to essential medicines (TOLEDO et. al., 2003).

From a socioeconomic perspective, it is necessary to highlight some aspects such as the demand for phytotherapy and the cost of the medicines, the potential for generating occupation and income in the phytopharmaceuticals productive arrangement, especially under the social economy, the efforts of research that prove, scientifically, the medicinal properties of plants, and the need for restructuring the health care system, including the preparation of professionals working in this area (NUNES et. al., 2003).

The recovery and revaluation of the use of medicinal herbs in Brazil today are demanding a certain worry since many medicinal plants of high value may disappear from the forests and scrub lands, even before scientists can discover their properties, and turn them into medicines. The main step that must be taken is to develop techniques for cultivation and harvesting without compromising the reproduction of these species. Another measure is to prevent urban sprawl from causing the destruction of peripheral green areas which are rich in medicinal herbs (ADEODATO et. al., 1996).

Medicinal plants, which have assessed their therapeutic efficacy and toxicology, or safety of use evaluated, among other properties, are scientifically approved to be used by people in their basic health needs, according to the ease of access, low cost and compatibility with cultural traditions. Since medicinal plants can be classified as natural products safe to use, the law allows them to be marketed by notification to the health regulatory agencies (BRAZIL, 2010), and they can be cultivated by those who follows agronomical good practices. So, the assisted self-medication is practiced in cases of health problems that might be considered simpler and more commonplace within a community. This practice tends to reduce the demand for health care professionals, rationalising and reducing the cost of Public Health Service (LORENZI & MATOS, 2002).

Despite these recommendations, it seems that the use of medicinal plants in public health service is still not a reality in different localities in Brazil and, by extension, in the American Continent. This fact can be explained by the lack of scientific data on native species or the lack of systematization of the existing data. The lack of political interest signals that this issue is not a priority for many governments in different parts of the world. As long as the practice of phytotherapy does not bring financial rewards, private capital will not feel encouraged to invest in this niche of market, which meanwhile is interested in more profitable and less regulated activities.

1.1 Techniques and methods for selecting medicinal plants

In the investigation of medicinal plants, a relevant moment, which can set the course of the work and its impact on all points of view, is the criterion used for the selection of the plant species to study. Cuéllar and Guirado (2008) refer to genomics, metabolomics and ecological, botanical taxonomic and epidemiological based studies. On the other hand Albuquerque and Hanazaki (2006) point out other ways to study the medicinal plants, among which we highlight five basic types of approaches: the randomized, the ethological, the chemotaxonomic (also known as phylogenetic or chemosystematic), the ethnodirected (or ethno-oriented) and finally, the exploration of promising biological test results (ELIZABETSKY; SHANLEY, 1994).

Some of these options are analyzed below.

1.2 The randomized approach

Several important authors, here mentioned, recognize the randomized approach as an approach without criteria. Calderon (2000) and others who worked with forest plots, do not identify this form of selecting plants for research, as random. So, the question here to be discussed is whether it is a type of random selection criterion or whether it should be identified separately as another type of approach?

The randomized investigations consist in random selection and collection of plant species for study, according to the plant availability. When carried out in regions with high diversity and endemism the probability of finding novel substances, bioactive or not, is certainly higher in this type of selection (MACIEL et al., 2002, OLIVEIRA et al., 2010). It is an indispensable approach, once it can demonstrate the potential of different plant species that had never been investigated. According to Souza Brito (1996), this type of selection provides an endless source of new structures, since nature is a vast chemical laboratory. However, there are many mistaken views and criticisms about this approach due to its randomness, which does not mean the absence of criteria (ALBUQUERQUE, HANAZAKI, 2006).

1.3 The ecological approach

The ecological approach, also known as *field observations*, consists in observations of interactions between organisms in their ecological environment, inducing to potential biological activity (antibacterial, antifungal, agrotoxic, pesticide) (GUIRA; CUÉLLAR, 2008). This approach searches for secondary metabolites and biological activities and it may be performed by the selection of young leaves x mature leaves for a given species, or between different species that are shadow resistant and not shadow resistant, among other characteristics (COLEY et al., 2003), though little explored, it has achieved excellent results.

Briskin (2000) states that secondary metabolites present in plant species have ecological functions which can justify their use for application in the development of therapeutic resources for humans. For example, metabolites involved in plant defense against microbial pathogens may be useful as antimicrobial drugs in humans, since they are not very toxic. Likewise, secondary products with repellent action (e.g. unpleasant flavor or odour) against herbivores by neurotoxic activity could have beneficial effects in humans such as antidepressants, sedatives, muscle relaxants or anesthetics, through their action on the CNS. Therefore, the observation of these ecological relationships is a useful tool in the selection of plant species.

According to Albuquerque and Hanazaki (2008) this approach intends to evaluate the use of secondary metabolites by animals or other non-nutritional substances from plants, aiming to combat diseases or controlling them, as it can be seen in the works developed by Carrai (2003) and Krief (2004). In the latter, it was observed that leaves of *Trichilia rubescens* Oliv. eaten by chimpanzees in Uganda showed antimalarial activity. This result shows the importance of the ethological approach in the discovery of useful plant species of medical and pharmaceutical interest.

A variation of the ecological approach is zoopharmacognosy, also called animal self-medication (self-medication in animals), which proposes the selection of species regularly ingested by animals, especially primates; to reduce microbial infestation, pain (BERRY;

MCFERREN; RODRIGUEZ, 1995. In: BIRD; BRIJESH; DASWANI, 2007). To the selection criterion based on the observation of the relationship between animals and plants, Albuquerque and Hanazaki (2008) attribute the term "ethological approach" based on the habits of animals, how they behave in their natural environment.

1.4 The chemosystematic approach

When the definition of a plant species, which will be source of a phytomedicine, is based on the structural analogy of the substances present in this plant material, with other known active substances present in different botanical family, genus or even species, we can infer that this strategy is based on chemosystematics, a system created by Professor Otto Richard Gottlieb (1982) to organize and understand the plants. This system consists in identifying groups of chemicals present in plants, considering the taxonomic organization of these plants. To illustrate this topic, consider the use of a plant species containing antiplasmodic indol derivatives as active principle in the development of an antimalarial phytomedicine.

Would a plant species from a different genus, containing such substances, give origin to the same phytomedicine?

Depending on the results the later plant produces in *in vitro* biological tests, it may be true. On the other hand, *Mikania* species (Asteraceae) which contain coumarin in their composition, exhibit different pharmacological activities and alleged popular use, including antimalarial properties. Therefore, the strategy based on chemosystematics can bring in it some uncertainty, once the chemical composition, which can explain the relationship between botanical species, genera and even families, is not decisive enough to guide the development of a phytomedicinal product and to validate the alleged use, as well as it does not confirm the safety and efficacy of the derivative proposed for the development of the product, requiring indeed the realization of a pharmacological prospection in order to characterize the wanted activity for the phytomedicine. The contribution of chemosystematics is to offer to the phytochemical analyst a range of possible chemical structures to be searched in the preparations obtained from the plant material.

The chemosystematic approach, also called phylogenetic, consists of selecting a species from a family or genus, for which some phytochemical knowledge of at least one species of the group is known (ALBUQUERQUE, HANAZAKI, 2006). The presence of different compounds, which can be used as biosynthetic markers, is used by botanists in taxonomy studies and the chemosystematic approach is used as a successful tool in the selection of families, subfamilies and genera to be investigated in terms of produced metabolites (BASSO et al. 2005). That is, through the chemotaxonomy, one can select plants from known families and genera to produce certain classes of substances (e.g. alkaloids, flavonoids, steroids, etc.), especially those recognized by their biological activities and therapeutic applications, preferably associated to these metabolites. As an example we can cite the case of galantamine, used in the treatment of Alzheimer's disease, first isolated from the species *Galanthus nivalis*, Amaryllidaceae family. Since then, numerous chemosystematic studies verified the presence of galantamine and acetylcholinesterase inhibitory activity in several species of the genus *Galanthus* (MARSTON; KISSLING; HOSTETTMANN, 2002). Following the same line, Ronsted et al. (2008) continued searching for alkaloids with acetylcholinesterase inhibitory activity in several species of other genera of Amaryllidaceae family, especially *Narcisus*, obtaining excellent results.

Considering that in this case we deal with the selection of plant species for the development of herbal medicines or for direct use in primary health care, this feature of the method, enabling the discovery of molecules, does not influence the discussion and treatment of the theme in this chapter, without, however, making value judgments on this important application. Even within the pre-formulation studies carried out during the experimental stage of drug development it is an advantage for researchers to know in advance which class of metabolites to prospect in order to develop detection, characterization and quantification of markers of the active pharmaceutical ingredients and the final product, and with these data to establish their quality control process. This step of the process is determining for the registration of an herbal medicine in Brazil.

2. The ethnoguided approach

The ethnoguided approach consists of selecting plant species in accordance to the indication of specific population groups in certain contexts of use, emphasizing the search for the locally built knowledge regarding their natural resources and their application in their health systems (GUIRA; CUÉLLAR, 2008). Plant species are raised by a quali-quantitative survey. This survey usually relates symptoms, signs and diagnosis of low-gravity diseases to medicinal plants that the respondents know about and their use according to the cultural elements that characterize the ethnicity or human group to which they belong, considering the territory as the basis for this characterization.

In this type of approach the ethnobotany, ethnopharmacology and ethnomedicine can be highlighted. Recently ethnopharmacy has been structured to provide an interface between Pharmaceutical Science and Popular Phytotherapy where medicinal plant species can be selected for the development of phytomedicines and for use in primary health care, in compliance with the requirements of safety and efficacy (BARBOSA, 2008).

Below we schematically present the key steps for developing an herbal medicine considering as a starting point the selection of a medicinal plant according to the ethno-oriented method. Note that the remaining steps of the process do not allow a review of the plant identity, once they are irreversible and consume the collected and processed plant material, making its selection and identification a crucial step of the process as a whole. In Figure 1 below, Material Plant, Crude Extract and Standardized Extract, direct derivatives of the medicinal plant, are shown in the purple sequence. The procedures to which these materials are subjected are in green and the blue area shows the pharmacological assays. Note that both standardized extracts as well as fractions of these extracts can be pharmacologically evaluated and taken to the formulation step where the composition of the active pharmaceutical ingredient will determine the pharmaceutical form to be developed and the experiments required for this procedure.

See below a schematic sequence of processes for developing phytomedicine (Fig.1).

In Brazil, the National Health Surveillance Agency accepts ethno-oriented surveys as the basis for the registration of plant species which are used for the development of herbal medicines (BRAZIL, 2010) or for use in primary health care (BRAZIL, 2010b). The methods applied in these surveys produces plant species lists and information that provide the starting point for developing a formulation, when their allegation of use are already available. It is also associated with a historical use of the plant, often for a long period,

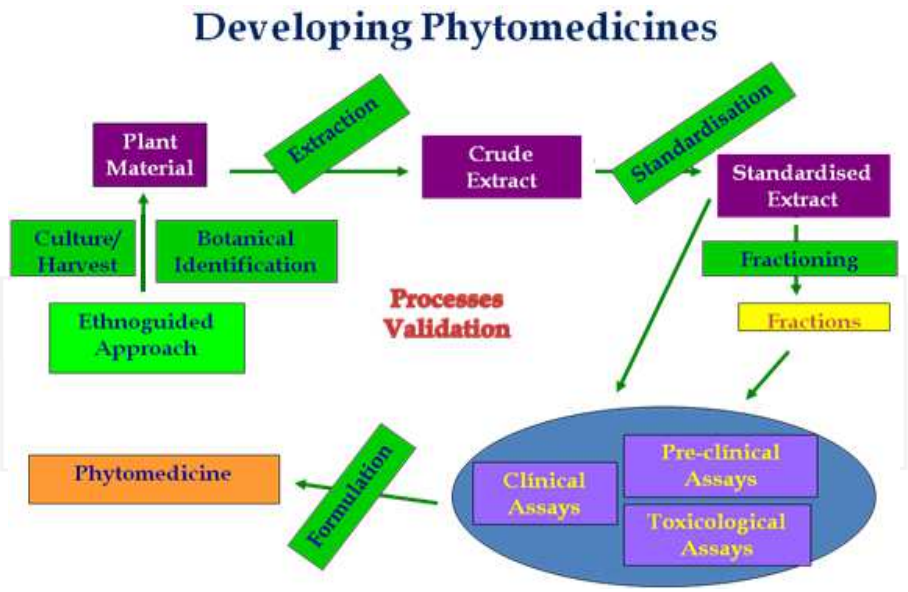

Fig. 1. Schematic sequence of the steps in developing phytomedicines, starting from an ethnoguided survey.

which being documented by scientific literature can contribute to validate its safe use based on official resolution. These requirements serve as the basis for the necessary experiments for pre-formulation studies.

2.1 Ethnobotany

Defining a medicinal plant for developing a phytomedicine under the vision of Ethnobotany, a survey of plant species used by a particular human group, certainly ensures botanical classification of the plant, since the core activities of Botany is to determine the taxa of a botanical sample. Moreover, important information for the production of plant material for the development process could also be provided by this approach. However, information like remedies preparation, allegations of use, including dosage, and evaluation of the remedy use and the relationship between user and derivatives prepared with plant material, are not part of the necessary instrumental for the practice of Ethnobotany.

In order to introduce a discussion on the survey of medicinal plants which are traditionally or popularly used for medicinal purposes, and within a historical perspective, this is what the Ethnobotany is about, a term coined by Harschberger and, which according to Schultes, pointed out ways that could serve to the scientific research (SCHULTE, 1962). Amorozo & Gely (1988) complement that ethnobotany, when applied to medicinal plants, acts in complicity with ethnopharmacology and medical anthropology, as it contextualizes the use of these plants in a treatment system peculiar to a specific human group.

According to Heinrich and Bremner (2006), the ethnobotany investigates the relationship between humans and plants in all its complexity, and is usually based on a detailed

observation and study of the plants used by a society, including all its cultural beliefs and practices associated with that use. For such research, the ethnobotanists use a complex set of methods derived from the social and cultural sciences, including the taking of detailed field notes and the carefully documented collection of plant samples that allow a precise determination of the corresponding species.

Regarding the ethnobotanical approach method, Elisabetsky (1987) and De La Cruz Mota (1997) advocate the devolution or the return of prepared data to the communities and Martin (1986), supports the inclusion of the communities in the research so that the constant ethnobotanical making will promote the development and preservation of plant resources, knowledge of nature, the restoration of ecological balance with improved life quality. One must still think about the profits arising from the business performance of the technological development, which starts with the study of the ethnobotanical knowledge, whether in form of royalties or compensation to the communities participating in the research.

2.2 Ethnopharmacology

The relationship with the environment makes different human cultures absorb a wide variety of customs and knowledge from this environment in which they live. This knowledge evolves and over time is incorporated into the patterns of each population group across generations. The most representative and discussed case at a global level is the use of natural products arising from the knowledge of traditional peoples as Indians or riverbank people. In this case, a greater attention is given to those people who live in tropical regions where the natural range of options is presented in higher proportions, as in the Brazilian Amazon (PINTO & MADURO, 2003).

The most accepted definition of *Ethnopharmacology* is "multidisciplinary scientific exploration of biologically active agents traditionally employed or observed by man" (SOUZA et al. 2004). Another useful definition was proposed by Dos Santos & Fleurentin (1990) as an "interdisciplinary scientific study of materials from animal, vegetable or mineral origin and related knowledge and practices that different cultures use to modify the state of a living organism by therapeutic (curative/prophylactic) or diagnostic purposes". According to Bourdy (2008), many ethnopharmacological studies seek to correlate pharmacological activities found in a traditional remedy with active pharmaceutical ingredients through natural products chemistry. Ethnopharmacology, therefore, in its interdisciplinary nature, attempts to associate at least three points of view, a cultural, a biological and a chemical ones in a complementary approach.

The Ethnopharmacology seeks to know the illnesses that lead particular human groups to practice Herbalism; it discusses symptoms and signs, as well as, experimentally, applies pharmacological models to elucidate the action mechanism of phytoderivatives. This information is also very important for the development of herbal medicines, but the evaluation of the original form of use is decisive for the elaboration of the phytopharmaceutical formulation, moreover, it allows the use of medicinal plant *in natura* or in magistral or officinal formulations, after pharmaceutical manipulation in pharmacies.

The ethnopharmacological method combines the study of popular knowledge with chemical and pharmacological techniques. Allegations of popular therapeutic use of a particular plant

species are important for the investigation of its pharmacological and toxicological effects (ELISABETSKY, 2003).

Albuquerque and Hanazaki (2006) claim that the ethnopharmacological approach is the study of traditional preparations used in health systems and disease, which include, isolated or combined, plants, animals, fungi or minerals. According to Maciel et al. (2002), on this approach the selection of species is carried out according to the therapeutic use evidenced by a particular ethnic group and it most likely favors the discovery of bioactive substances, the development of herbal medicines and the introduction of medicinal plants in primary health care. Many studies based on ethnopharmacological approach, report results that range from strictly botanical information, such as plant taxonomy, to general information such as part of the plant used and alleged use (UBOM, 2010; GIUSTI & PTERONI , 2009; IGNACIMUTHU et al ., 2006; GIDAY,. 2001).

Ethnopharmacological strategies have been widely used to conduct biological screening in various therapeutic areas such as cancer, immunomodulatory drugs, allergy drugs, analgesics, contraceptives, antimalarial, anti-diarrhea, antimicrobial, antiviral, etc. (ELIZABETSKY; SHANLEY , 1994).

Ethnopharmacology, an important methodology for the study of plants used in folk medicine, is characterized as a strategy for the investigation of medicinal plants that combines information acquired from users of medicinal plants with chemical and pharmacological studies. This method, still according to Elisabetsky, allows the formulation of hypotheses about the pharmacological activity and the compound responsible for the reported therapeutic action. Elisabetsky says "Ethnopharmacology is not about superstitions, but of popular knowledge related to traditional medicine systems" (ELISABETSKY, 2003).

2.3 The ethnomedical approach

The Ethnomedicine refers to the study of diseases, their causes and therapeutic measures taken by the various societies of primitive peoples as well as by popular social communities. It deals with natural and ancient therapies used to combat diseases and emphasizes the relationship between the patient and caregiver, between the patient and society. Ethnomedical studies contribute to the knowledge of the techniques used by many ancient peoples with regard to the treatment and knowledge of diseases (BENSON, 1980).

Since ancient times people treated their body and soul illnesses by asking for help to the supernatural. Certain peoples of northern Asia, where the tribal priest was called the shaman, used magical means, rites and knowledge of nature to heal health problems, associating them, among others, with knowledge about healing plants and connecting with their gods. So, they antagonized the disease with the active ingredient of the plant and with the ritualistic method, they incited the faith, the confidence in the procedure and in the shaman, who, in Brazilian Amazon, is called “pajé” or “benzedor” (shaman healer), according to more or less intimacy with the ”enchanted" and the "forest spirits" (MAUES & VILLACORTA, 2008).

A significant part of what today is therapeutically used, started from information obtained from traditional communities that use natural products in their practices to survive and handle the environment. According to Guirado and Cuellar (2008) the ethnomedical

approach consists in investigating the plant species on the basis of traditional use by different peoples, providing an interface between modern clinical medicine and folk medicine.

2.4 Ethnopharmacy

The strategy that can gather more information directly linked to the galenic development of a phytotherapeutical formulation is the ethnopharmaceutical approach of medicinal plants. Here, the semi-structured interviews script allows assessing, among other, the nosological profile of the approached human group and the medicinal plants used to treat the signals and symptoms mentioned by the interviewers. The method also evaluates the utilization of synthetic and herbal medicine by the group, and proposes the participatory observation of the remedies preparation using the most promising plant and finally observes aspects related to the plant itself. In this way it is possible to characterize the needs of this human group in terms of products which solve most of its health problems, this can be seen as a market analysis under the pharmacoeconomics point of view; also under this perspective, it is possible to determine the scale of this demand, verifying which synthetic medicines are not accessible to users and which herbal remedies they prepare to meet the lack of those products which are not distributed by the market (open or State), and also by observing the preparation of remedies by the community, a pharmacist can deduce a pharmaceutical form for the product under development and discover new procedures, as well as new pharmaceutical adjuvant.

For Heinrich (2001), the Ethnopharmacy is the interdisciplinary science that deals with the study of pharmaceutical resources considered in relation to cultural determinants that characterize the use of these resources in a particular human group. It involves studies on the identification, classification and cognitive categorization of plant material from which the drug will be produced (Ethnobiology), preparation of dosage forms (ethnopharmaceutics), allegation of the effects associated with the preparation (ethnopharmacology) and socio-medical aspects implied in these uses (ethnomedicine) (PIERONI et al., 2002).

Heinrich (2007) returns to the subject stating that ethnopharmacy includes pharmacognosy, pharmacology, galenic, and also the pharmaceutical practice and clinical pharmacy, thus allowing the utilization of local resources in the primary health care, and therefore it provides an interface to the Pharmaceutical Assistance necessary to the implementation of Phytotherapy in Primary Health Care.

The ethnopharmacy was introduced in Brazil in 1995 with the publication of the article "Ethnopharmaceutics: an approach to medicinal plants from the perspective of Pharmaceutical Sciences" (BARBOSA, SILVA, SOLER, 1996). The inventory of data from a group or local community on therapeutic resources shows itself as an adequate tool to document important information to design actions in the Pharmaceutical Sciences area, both from a technological standpoint as for healthcare, since it allows to obtain information about infectious diseases, the appropriate medicinal plants indicated for their treatment and it infers the most suitable methods for their preparation and use (PINTO, 2008).

In Brazil, Ethnopharmacy is defined as an interdisciplinary science that investigates the perception and use of traditional remedies, within a human group. It deals with the study of pharmaceutical resources considering the relations with the cultural context of its use, or the

study of cultural determinants that characterize the uses of these resources in this culture. This study involves plant ethnotaxonomy, by which the drug is produced; the preparation of popular use form (ethnopharmaceutics); the biological evaluation of the pharmacological activity of such preparations (ethnopharmacology); clinic ethnopharmacy; medical anthropology or ethnomedicine; pharmacotherapeutic follow up and pharmacosurvaillance.

As a set of materials and practices used to maintain and restore health within a regional cultural context, several papers have been published; Bulus (2003) reported the ethnopharmacy of malaria in Nigeria; Pieroni (2005), the therapeutic resources of a community rooted in the northern Albanian Alps; he has raised about 70 taxa and 160 preparations; Thabrew (1991) described three species used as immunomodulators in liver disorders, in traditional herbal medicine in Sri Lanka. These papers report surveys conducted according to the ethnopharmaceutical methodology.

The ethnopharmaceutical method was developed by integrating environmental and cultural elements, thereby becoming a strategy for preserving the cultural heritage of human groups and actions for recovering deforested areas (BARBOSA, 1998).

Souza (2011) proposes the Ethnopharmacy as a science that permeates across the ethnosciences related to medicinal plants, especially regarding their use, articulating it with those belonging to the identities and cultural imagery of the focused human groups. Ethnopharmaceutical science seeks to understand the use of medicinal plants through the social representations of communities based on the oral diffusion of knowledge about the community's relationship with the environment, availability of medicinal plants, as these representations are keys to the establishment of the safety validation process and rational use of medicinal plants

Thus, we propose two strands to the ethnopharmaceutical methodology: as a science (where there is an object, methodology and production of knowledge) and as a social technology where it develops products, methods and services together with communities, replicable in other communities, aimed in improving their life quality and favoring their social inclusion.

To illustrate the proposal presented above, we show the figure 2 below that tries to characterize the composition and the insertion of Ethnopharmacy in the science and technology fields and thereby demonstrate the breadth and scope of its instruments when applied in Popular Phytotherapy survey, with the aim of pointing out plant species for phytomedicine development and their use in primary health care.

The ethnopharmaceutical survey is an instrument of the quantitative research advocated by the social technology Ethnopharmacy, which brings together a methodology and a theoretical basis to leverage the popular herbal medicine as a basis for Pharmaceutical Attention in medicinal plants, after processing of the collected data by the Pharmaceutical Science.

The contribution of accessed human groups is significant, as well as the participation of the academy and the public sector; the participation of the private productive sector is still lacking, which, in Brazil, needs to adequate its action and thought to the national sanitary surveillance rules in order to contribute in building this important economic and social sector that is the market for herbal medicines.

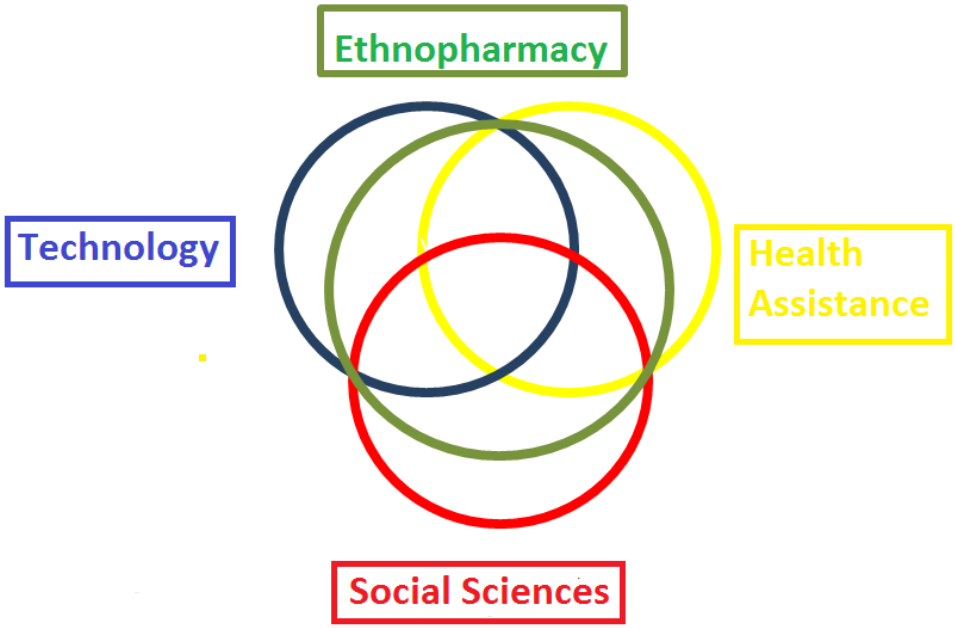

Fig. 2. Representative diagram of the interdisciplinarity of Ethnopharmacy.

Fig. 3. Meeting of researchers in Ethnopharmacy of Para Federal University with members of local collectivities, including traditional specialists, discussing the local phytotherapy (Igarapé Miri, Para, BR)

2.4.1 The ethnopharmaceutical approach and the use of flora

Different methodologies have taken into account the human and cultural component in their survey and approach of plant species with therapeutical popular use. The ethnobotany and ethnopharmacology dispute the antiquity: there are still ethnomedicine, the ethnobiology and there are others emerging.

In the development of herbal medicine, ethnobotany and ethnopharmacology play an important role towards this approach when aiming the popular information retrieval, the empirical knowledge which has been transmitted from generation to generation by shamans and healers in all cultures and traditions. The ethno-oriented survey puts the popular information as an important reference for the experiments both with regards to the exploitation and use of herbal drugs and phytomedicines, as well as for the development of new remedies.

Following this track, the instrumentation of methods and techniques has been established in the pursuit of a unique language that features not only recognition but also the application of traditional knowledge about plants and/or healing practices. One should also take into account the idea that the notion of illness and healing practices are understood through cultural references. In this context it is assumed that there are subjective factors related to the values and traditions of individuals and cultures that influence the formation of symptoms and how to treat them. This is therefore, the track that leads to the concept of the ethnopharmaceutical approach, demarcated on its roles and joints to other research areas by the objectives (BARBOSA, 1996):

- To understand the cultural meaning of a given disease and its healing process in a given community;
- To raise the traditional use of plant species in these communities while observing the social anthropological view, the inter-relationship of possible medicinal effects, their use in food and involved ritual habits as therapeutic tools for treatment of diseases;
- To recognize the plant species used, their botanical and popular nomenclature;
- To recognize in the traditional remedy the pharmaceutical form involved in its preparation;
- To prepare, in an interdisciplinary way, a method to exploit the species involving from cultivation to marketing;
- To propose, based on the plant investigation, from the scientific point of view, new applications for the species, either through pharmacological, biological and/or suitable technological approaches in the Pharmaceutical Sciences field;
- To standardize the pharmacognostic, phytochemical and pharmacotechnical protocols for regulation and quality control in the marketing and use of herbal medicine, among others;
- To produce knowledge from the results obtained during the development and use of the investigated medicinal plant.

The cultural elements of the community, related to fundamental traditional healing practices regarding the use of plant species, have been undergoing a process of devaluation, even discredit, due to the scrapping of medical care, caused by political and economic reasons. Moreover, the easy access to the allopathic medicine, encouraged by official policies of distribution of these drugs without proper pharmaceutical care, has led, even in

communities with ancient traditions, such as indigenous peoples, a depreciation of the traditional healing practices, so that the only alternative that remains to the ordinary member of the community is to ingest the industrial drug according to color or flavor, with the (dis) orientation of hardworking, but unprepared people for this important task.

In this context, briefly exposed, because it is matter for reflection in a specific chapter, the ethnopharmaceutical approach comes as an element of preservation and appreciation of traditional therapeutic practices, since all the experimental work is based on valuable information gathered from the plant user. This information is firstly systematized and documented, making it possible to provide a memory of the practices and the empirical knowledge of people about the plants used therapeutically.

The empirical statements, allegations of a plant use, refer to symptoms that correspond to a pharmacological test model, which can validate the indication of the preparation traditionally used obtained according to pharmaceutical techniques properly deduced from the popular mode of preparation. These data, together with those obtained from the chemical analysis of the plant, will enable to propose a defined therapeutic formulation containing a biologically active extract or an active fraction of this extract, ingredient that may be monitored for quality because it was chemically analyzed and presents the original activity properly quantified (effective dose and "toxic" or lethal dose) indicated by the community.

Among the information collected from communities, one should consider and seek to interpret the apparently unimportant data related to the symptoms described, to the collection of plant material, to the preparation of the medicine and to the usage of this drug. These data may be critical to the success of the experimental work. Details concerning these apparently mystical aspects of the plant use may indicate some procedures to be followed when preparing the material for testing and analysis, so it should not be seen merely as superstition.

2.4.2 Data produced from selected species according to the ethnopharmaceutical method

An ethnopharmaceutical survey conducted in 2008 in the State of Pará, Amazonia, Brazil showed that an Iridaceae (*marupazinho*) was indicated to treat diarrhoea, anaemia and abdominal pain.

Alleged use	Medicinal Plant	RAUPF
Anaemia	*Pariri*	100%
Verminoses	*Caxinguba*	100%
Flu	*Lemon*	88%
Diarrhoea	*Marupazinho*	79%
Rheumatisms	*Ginger*	75%
Headache	*Rue*	70%
High blood pressure	*Garlic*	67%
Gastritis	*Pirarucu*	50%
Fever	*Catinga de Mulata*	42%

Source: from Pinto, 2008, (yet unpublished data).

Table 1. The alleged medicinal uses of plants according to the relative frequency of alleged use (RFAU) calculated according to Amorozo & Gely (1988).

Combining these symptoms and adding information obtained from a traditional specialist we can infer that this plant could be used to treat amoebiasis (yet unpublished data). Indeed, in the Amazon region this plant is an important therapeutic option, used in primary health care. Jardim et al (2007) had demonstrated the use of a tea from the bulbs of this plant in the popular phytotherapy, to treat diarrhoea. The here mentioned ethnopharmaceutical survey discloses a convergence of popular use (AMOROSO; GELY, 1988) of about 80% for diarrhoea (Table 2), which rises to about 100% when other symptoms of amoebiasis are associated. These surveys were carried out in different cities of the state of Pará. Additional phytochemical and galenic studies were performed and a formulation will soon be developed; furthermore, the data already obtained can indicate the plant to be accepted as a medicinal plant of interest to the Brazilian primary health care system (BRASIL, 2010).

An ethnopharmaceutical approach started a multidisciplinary study on a Piperaceae and an Euphorbiaceae and enabled the development of formulations to control arterial hypertension and to treat bacterial skin affections, whose patenting processes are in course.

A Bignoniaceae mentioned by virtually all respondents, more than 1,200 people (Table 1), as having anti-anaemic activity, also shows important antifungal activity on skin affections (BARBOSA, 2008) among others. After the extract administration in animals, the haematological parameters were evaluated in their collected blood samples. The extract did not affect the following parameters: leukocytes, red blood cells, haematocrit, haemoglobin, MCV, MCH and MCHC, however, a significant increase in platelet counts for the experimental group could be observed, what can indicate that the aqueous extract stimulates the production of platelets (yet unpublished data) (Table 2).

Haematimetric Index	*Control group n=20*	*Experimental group n=20*	*P* value*
Haemocyte (/mm^3)	5.7±1.6	6.2±0.9	0.6423
Haematocrit (%)	41.3±9.2	41.5±3.7	0.4525
Haemoglobin (g/dL)	13.8±2.7	13.7±1.1	0.4275
MCV (fL)	50.2±2.7	51.6±1.9	0.1555
MCH (pgL)	16.5±0.7	16.9±0.7	0.2164
MCHC (g/dL)	33.1±1.2	33.09±1.6	0.9427
Platelets (mm^3)	702±244	888±201	0.0498

Table 2. Haematimetric indices and platelet counts of animals exposed to plant extract and the control group. Hematologic parameters of control group are similar to other studies in which the same strain of mice was used, and corroborate the study by Pessoa et al. (2008) that observed the lack of significance between hematological parameters of *Rattus norvegicus* treated with plant extract.

The approximation of ethnopharmacy with pharmaceutical care provided the establishment of a new attribution to the ethnopharmaceutical method, namely: the selection of popular medicinal herbs for introduction in primary health care. *Eleuthrine plicata* (BRAZIL, 2009), *Arrabidea chica* (BRAZIL, 2011) and *Zingiber officinalis* (BRAZIL, 2010B), are species listed in official documents that have been related in ethnopharmaceutical surveys conducted in different localities in the Amazonian state of Pará.

3. Comparison between the randomized and ethnoguided approach

It is expected that the traditional knowledge about medicinal plants indicates the presence of biologically active substances. The collection of plants traditionally used for biological assessment can be a great advantage, or a shortcut, increasing the chances of discovering new drugs (ELIZABETSKY & SHANLEY, 1994). Table 3 shows the enormous potential of the ethnopharmacological approach found in several studies, compared with the randomized approach.

Some studies have compared the results obtained by the random selection of plants with the ethnopharmacological approach, also called ethnoguided approach. In Rwanda, Africa, 100 medicinal plants were tested for antimicrobial activity. From these, 68 were referred for infectious diseases, 37% of which were active, whereas for the 36 medicinal plants that were included by the random approach only 22% showed activity (VAN PUYVELDE & BOILY, 1986). In another study conducted at Sinai (Egypt) for plants with antimicrobial activity, 83.3% of the species obtained positive results by the ethnoguided approach against 41.7% in the randomized approach (KHAFAGI & DEWED, 2000). In Brazil, a study of antimalarial activity performed with extracts from 295 plant species, 273 were tested by a randomized approach with only 0.7% of positive results, whereas for the 22 medicinal plants with indications for fever and malaria the positive results represented a total of 18% (CARVALHO & KRETTLI, 1991). In Belize, Central America, random collections of plants sent to the National Cancer Institute (NCI, USA) for anti-HIV activity resulted in 6% of active samples. However, with ethnopharmacologically selected samples, from a healer in a small village in Belize, an activity of 25% was obtained, showing a percentage four times higher (GUIRA & CUELLAR, 2008).

BIOLOGICAL ACTIVITIES	RANDOM (%)	ETHNO (%)
Antineoplasic	6	25
Antihypertensive	31	44
Anthelmintica	9.8	29.3
Ichthyotoxicity	9.6	38.6
Toxic/venoms	10.5	52.2
Anti-HIV	8.5	71.4
Antimicrobial	22	37
Antiplasmodial	0.7	18
Acetylcholinesterase inhibition	8	42.3

Source: from Oliveira et al.

Table 3. Comparison between the numbers of hits achieved by Ethnopharmacological x Random approaches in the search for different biological activities (OLIVEIRA *et al.* 2011).

Slish and colleagues (1999), when evaluating plant extracts obtained by the ethnoguided method (n = 31) for the relaxation effect in rat aortic smooth muscle, had a score of 12.9% active species, whereas by the random approach (n =32) no active species were observed. In an assessment with 80 traditional medicine plants from Reunion Islands for angiotensin-converting enzyme inhibitory activity, which plays an important role in blood pressure regulation and diuresis, 44% of the species indicated by their antihypertensive or diuretic effect were active against 31% of the species without such indications (ADSERSEN & ADSERSEN, 1997).

The selection of plants for use in primary health care should be based on the nosology of the region, referred to in the Brazilian Policy for Phytomedicine and Medicinal Plants (BRAZIL, 2006), which is determined by an interview survey conducted among local experts in the communities . The nosological map obtained, defines the range of plants that are then selected according to technical criteria, considering their agronomic and pharmaceutical aspects. The list of the plants used to treat diseases that compose the nosological profile emerges from the treatment of the information provided by the respondents, applying the programming rule of the Pharmaceutical Assistance (BARBOSA, 2008).

4. Possible innovations in phytomedicine development from the ethnoguided surveys

The development of herbal medicines, as they need to generate specific parameters for each formulation, is more productive in terms of knowledge than in terms of the synthetic analogue, once the constitution of each species that gives rise to herbal medicines varies from one species to another. Compatibility studies of adjuvant in relation to the components of plant extracts, the need to characterize quality markers, pharmacologically active or not, all this set induces a creative process marked by strong innovative character. Some topics are presented below:

- Regulation of pre-products and insumes; in the legal-administrative sphere, the phytomedicines bring and impose the need to develop regulatory frameworks that do not exist in many countries.
- Documentation of traditional knowledge in the form of a regionalized National Plant Pharmacopoeia; in continental countries like Brazil, or which have microclimates with different biomes, this is a remarkable feature, and the existence of national human groups with appropriate cultural heritage, possessing their own herbal knowledge also influences.
- Development of products to attend the national nosology; as a result of the ethno-oriented surveys which, besides the list of plants can generate a regionalized nosological profile; this profile guides the development of therapeutical formulations to treat local diseases, often neglected by large laboratories .
- Using the production of medicinal plants to recover degraded areas; to meet the national and local demands for plant material both for herbal medicines production as for use in primary health care, it is necessary to cultivate selected species, which can be intercropped and would not make sense to grow them in forested areas, but in areas that could be recovered.
- Involving the communities in the production projects; since it is an ethno-oriented process, it involves communities *per se*; in the case of Ethnopharmacy, a social technology, the involvement of organized human groups is higher and can trigger initiatives.

- Applying new methods for development; the partnership of the academy in the development of phytomedicines, required due to the low participation of the pharmaceutical productive sector in this process, induces the application of modern techniques, as the academy, apart from contributing to the process still needs to produce knowledge in accordance to the regulatory sector.

5. Medicinal plants in the basic health care from ethnoguided approach

In Brazil the traditional use of medicinal plants was recognized by the public health administration and was integrated into the official health system through the National Policy of Complementary and Integrative Practices (BRASIL, 2006b).

To support this therapeutical option available to the general population that uses the Integrated Brazilian Health System (SUS), regulatory documents were elaborated and promulgated which present a list of medicinal plant species of popular or traditional use, selected on basis of a set of information that indicates and supports the alleged use of these plants, its form of use and the cares to be taken in the preparation and the administration of the therapeutical product.

The information that substantiates the inclusion of a given medicinal plant species into the primary health care is carefully conferred in the scientific literature. Data on botanical, agronomical, pharmacognostic and chemical characteristics are checked for the unequivocal description of the plant material to be considered as a potential source for an officialised phytotherapeutical. Results concerning the effectiveness and security of the herbal drug or its derivatives as well as information about toxicological, pre-clinical and clinical investigation of the plant species, herbal drug or preparations obtained from them, complete the set of data. So, in this way, medicinal plant species are inserted into the list of phytotherapeutical for use in the basic health attention. Nowadays vegetal species and derivatives species are available as therapeutic resource in the basic pharmaceutical assistance program.

Since information about a given medicinal plant species is still to be produced, the plant is inserted in the national Relation of Medicinal Plants of Interest for the Integrated Brazilian Health System (RENISUS), where the medicinal plants species that present good potential to generate products of interest to the SUS, or plant species that can be incorporated into the Live Pharmacies (an official program of medicinal herbal gardens cultivated in units of basic health assistance) or generate phytotherapeutical (teas, tinctures, pomades or other simple pharmaceutical forms) are inserted.

The purpose of this list is to guide studies and research that can support the elaboration of a relation of available phytotherapeuticals for safe and effective use by the population, to treat some mild illnesses. Currently, "espinheira santa"and "guaco"phytotherapeutic derivatives are offered, respectively, for gastritis and ulcer, and for cough and influenza (BRAZIL, 2009).

In RENISUS there are 71 medicinal plant species with therapeutical potential to induce the development of research projects and to motivate organization of productive arrangements; which are disclosed by the National Programme of Medicinal Plants and Phytomedicines of the Health Ministry. Amongst these medicinal plant species *Cynara scolymus* (artichoke), *Schinus terebenthifolius* (aroeira da praia) and *Uncaria tomentosa* (cats claw) can be found,

which are used, according to the popular knowledge, to treat digestive disorder, vaginal inflammation and articulation pains, respectively, and whose indications are scientifically confirmed (BRAZIL, 2009).

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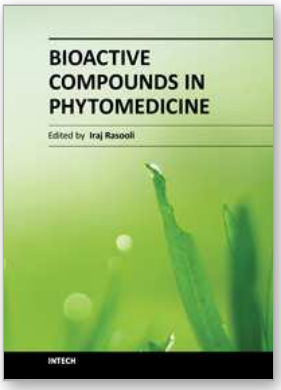

Bioactive Compounds in Phytomedicine

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There are significant concerns regarding the potential side effects from the chronic use of conventional drugs such as corticosteroids, especially in children. Herbal therapy is less expensive, more readily available, and increasingly becoming common practice all over the world. Such practices have both their benefits and risks. However, herbal self-therapy might have serious health consequences due to incorrect self-diagnosis, inappropriate choice of herbal remedy or adulterated herbal product. In addition, absence of clinical trials and other traditional safety mechanisms before medicines are introduced to the wider market results in questionable safe dosage ranges which may produce adverse and unexpected outcomes. Therefore, the use of herbal remedies requires sufficient knowledge about the efficacy, safety and proper use of such products. Hence, it is necessary to have baseline data regarding the use of herbal remedies and to educate future health professionals about various aspects of herbal remedies.

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Phone: +86-21-62489820
Fax: +86-21-62489821