

TRADE AND QUALITY CONTROL OF MEDICINAL PLANTS IN BRAZIL

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ABSTRACT

The use of medicinal plants is influenced by the cultural legacy of popular knowledge of plants with therapeutic purposes, resulting from the ethnic mix of the population, with a strong Indian, European, African, and Asian influence. Other factors, such as difficulties in access the regular health services associated with poor socioeconomic conditions, and easy access to medicinal plants, and/or herbal products have contributed to consolidate herbal medicine as a widely resource used by the population. However, these products, derived from plants do not always possess the sufficient safeguards for their use and have not been proved for their therapeutic safety or quality. Thus, it emphasizes the need for studies on the marketing of medicinal plants, and to evaluate the quality of these products in order to conduct pharmacovigilance, ensure safe and effective use, especially by contributing to the full development of Phytotherapy.

Keywords: Herbal medicines, Marketing, Medicinal plants, Pharmacovigilance, Phytotherapy, Natural products

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INTRODUCTION

Since the beginning of civilization, man is dependent on natural resources, especially of plant origin to heal, cure or prevent diseases [1]: aiming to preserve and maintain this medical practice, through a handling route, adaptation and modification of these resources for their benefit. It can be said that the habit of resorting to the healing virtues of certain plants is one of the first manifestations of man's effort to understand and use nature [2-4].

This practice of using natural, folk and, herbal medicine or phytotherapy, is the accumulation of knowledge, passed on from one generation to another, through the action of the plants used in healing and disease prevention. Each ethnic group has their knowledge about the therapeutic value of plants, and this is part of their cultural background [5].

Historically, it is recognized that this practice has been through several phases of representation in society. It contributed to form the therapeutic basis and to be the first and/or only therapeutic resource used for a large part of the world's population. Moreover, the usage of natural products is also considered the sideline for only use by the less benefited social classes without access to western traditional health services [6, 4].

In the current scenario, phytotherapy has been included in contemporary society, in both developed and developing countries has become integrated into many social classes, hence is not limited to the people living in rural areas or regions lacking health assistance [7].

According to World Health Organization (WHO), 70-90% of the population in developing countries rely on herbal medicines especially for primary health care, and the significant portion of the population from developed countries such as Canada, France, Germany and Italy also relies on therapeutic resources of plants and their derivatives [4]. This is due to better compatibility with the human body and lesser side effects associated with the use of plant-derived products.

This review aims to describe the trade of medicinal plants in Brazil, as well as discusses ways to perform the quality control of these products in order to promote their safe and effective use, and hence would contribute to the development of pharmacovigilance in herbal medicine.

This work was carried out in databases (Biological Abstracts, Chemical Abstracts, Medline, Lilacs, Web of Science, Science Direct, PubMed), as well as in the official compendium and dissertations and theses, covering the last thirty years until March 2016. The keywords in combinations used in this review were sensory analysis, authenticity, marketing, quality control, plant drug, pharmacovigilance, herbal medicine, health, herbal market, medicinal plant, traditional herbal medicine, purity, popular use.

Current scenario: use and trade of medicinal plants

Looking at the international scenario of pharmaceuticals and/or derivatives of medicinal plants, the significant increase in sales of herbal medicines has been noticed in Europe and the United States. In these places, there have been an annual growth [8] rates between 10-20%, and consumption is estimated of US\$ 14 billion per year. Back to the analyses of the domestic market for herbal medicines, studies indicate that there is a sharp rise in the consumption of plant-derived products. Although there is a high biodiversity of plants with a medicinal purpose in Brazil, few herbal medicine has been developed from the indigenous plants, and it is not easy to find manufacturing phytomedicine in drugstores. So that the majority of the Brazilian people prefer acquiring the medicinal plant in popular and informal fairs [9].

Several studies have indicated the factors affecting the high consumption of plant-derived products such as the difficulty of accessing to health service of people from developing countries and also because of sweeping green wave that takes people to use natural products as both food and medicines all over the world including developed countries. The other factor that uplifts the usage of plants with medicinal purpose is the scientific approach both to produce phytomedicines as well as

sources of active compounds to be used as drugs in pharmaceutical industries [10-12].

In Brazil, many factors are favoring the preservation of the use of plants for medicinal purposes and hence contributing significantly to the increased demand for herbal products. Some of these factors include the rich biodiversity, the cultural knowledge from people and the inequality in the distribution of resources for health, with a concentration of specialized services in urban areas, favoring a minimal portion of the population [2].

In this regards, it is timely and essential to expand the therapeutic offerings in Brazil, especially after the creation of the Unified Health System (SUS) with the aim of compliance with its basic principles. The adoption of various measures and regulatory actions have been established by the Federal Government to formalize the herbal medicine as an alternative and/or complementary health drug [8, 13, 14].

Herbal medicine in Brazil

As a regulatory benchmark for structuring and implantation of phytotherapy in Brazil, Federal Government has taken steps and initiatives, including the National Policy on Medicinal Plants and Herbal Medicines (PNPMF) and the National Policy on Integrative and Complementary Practices (PNPIC) on Unified Health System (SUS), both published in 2006 [13, 15].

As the consequence of these legal requirements, the government approved in 2008 the National Program for Medicinal Plants and Herbal Medicines. This program aims mainly to the implementation of PNPMF and its goals such as the enhancement of the productive chain of medicinal plants and herbal medicines, encouraging research and technological development in this area, training of professionals of the herbal medicine sector and include herbal products on SUS with safety and quality [16].

Another advancement in this area was the publication of the Ordinance 886, of April 20th, 2010 by Ministry of Health, which established the Live Herbal Pharmacies in the Unified Health System (SUS) [17]. This Ordinance was complemented by RDC No. 18 of April 3rd, 2013, that sets the technical regulations for good practices of medicinal plants and herbal products in Live Herbal Pharmacies [18].

Regarding the mandatory registration of industrialized herbal medicine in the Brazilian Regulatory Agency (ANVISA), this process started in 1996 with the first legislation requiring scientific studies to allow the trade of these products. Several updates of these standards have been published over the years and currently the RDC 26 of May 13th, 2014 regulates the registration and notification of manufactured herbal medicines, which are classified as herbal medicines (MF) and traditional herbal products (PTF). The difference between them is based on the way to ensure safety and efficacy, which is assessed through clinical trials or by the traditionalism of use, respectively [19].

This resolution is complemented by the Normative Instruction (IN) 02, of May 13th, 2014, which brings the lists of plant species for the preparation of herbal medicines or traditional herbal products of simplified registration [19].

The concepts regarding the main nomenclatures used in this area as a medicinal plant, plant drugs, herbal medicines and traditional herbal products are described in the mentioned legislation, especially the RDC 26/2014 [20].

Plant drugs that mean the dry form of the vegetable, medicinal plant or herbal medicine represent alternatives to programs of Primary Health Care to raise the therapeutic options. Moreover, these products are much cheaper to the population and also to governments that support these programs. In Brazil, one of these programs where the phytotherapy is quite used is the Family Health Strategy [12, 21].

Despite there are many regulatory laws to organize the practice of usage of medicinal plants in Brazil, many authors have identified some problems related to the safety of these herbal products traded in this country. It occurs due to the unawareness and/or erroneous

disclosure of the advantages of this practice and become worse when these herbal products have no standardization nor quality control. The lack of scientific studies to assure the effectiveness, safety, and quality of them is a significant health problem [22, 23].

This situation is aggravated by the tendency of a large part of the population acquiring products from plants in the informal market. It has also been documented that sellers with no tradition in the area, proving that this practice is a real risk of acquiring and using an inappropriate material for consumption, due to misidentification, erroneous indications of use, inadequate dosage, use of poor quality plants and toxic plants [8, 24].

However, we must emphasize that the acquisition of plants and their derivatives in pharmaceutical establishments is not entirely safe. Recent national studies have proven that the marketing at pharmacies and drugstores, which theoretically has the performance of technically qualified professional does not guarantee product offering with good quality [25, 26].

These problems expose the user, as said before, to a real risk of use of plants and its derivatives with poor quality. It could be solved if there were a serious process of qualification pharmaceutical operations in order to validate analytical methodologies for quality control and standardization of these products, and require the exercise of authorities in monitoring, surveillance and quality control of plant species marketed and used for therapeutic purposes [27].

In this context, studies carried out by Silveira *et al.* suggested that for the dissemination of monitoring programs and pharmacovigilance of medicinal plants [28] as well as herbal medicines. Herbal often contains a mixture of plants with few studies on toxicity and adverse reactions. These responses can be either caused by the chemical constituents synthesized by plant or adulteration, contamination, improper preparation or and inappropriate, irrational [29, 30]. In order to ensure the safe and rational usage of herbal medicine as an alternative and complementary option in the therapeutic, several problems should be overcome. It includes investment in herbal pharmaceutical research and development, effective laws, and regulations that promote responsible market and production of botanical products. The lack of studies with native plant species in several countries and on standardization of botanicals and evaluation parameters of quality of medicinal plants and their products should also be considered [22, 28, 31, 32].

Pharmacovigilance in phytotherapy: quality control of medicinal plants and their derived products

According to Mendes *et al.* pharmacovigilance can be defined as the science relating to the detection, prevention, evaluation and preservation of adverse effects or any other drug-related problems [33]. It aims to reduce the morbidity and mortality associated with drug use through early detection of security problems of these products to patients and improving the selection and rational use of medicines by health professionals [34].

Thus, studies aimed to evaluate the quality of medicinal plants and herbal medicines has become one of the importance area of research [25].

Balbino and Diashave found that despite the evidence of the increasing rise of marketing plants and their derivatives, studies to evaluate the certification of safe use are still scarce. The proper control of marketing in the street or public markets and health food stores is required to be carried out [35].

This way, the rise in the use of medicinal plants and their derived products should take place in a conducive setting with the practice of herbal medicine grounded in specific regulatory mandates, based on the Pharmacovigilance objectives, requiring [27] the commitment of governments to the implementation of strict guidelines. Despite the recognized importance of specific legislation, only about 66 countries, including members of the WHO, have some legislation to this practice [36].

Undeniably, WHO recognizes the increasing use of medicinal plants and, consequently, stimulates phytotherapy. Ensuring safe, effective

and rational use of plants and their derivatives, as well as the quality control certification is one of the biggest challenges worldwide. The concern about the quality of herbal medicines has been shown to health authorities and the people who use these preparations [37].

The use of any input of plant origin including whole plant, drug or traditional/herbal products and medicines require certification of efficacy, safety, and quality of products available for use. It may be provided by a set of measures such as the full exercise of quality control, with targeted efforts and resources to the development, validation, and application of analytical methodologies [38, 25].

The quality control of raw materials to be used in nature and/or as plant drug in extemporaneous preparations or to be inserted in the supply chain to obtain the herbal medicines should be based on botanical chemical, physical and biological analyses to investigate the authenticity parameters, integrity, and purity [14, 12, 39].

During the last decade, the expansion of domestic market of plant products for medicinal purposes has stimulated studies, focusing on the evaluation of authenticity, integrity, and purity of raw materials available to the population. It's worth emphasizing that this is the first work conducting a systematic review of quality control studies of plants for medicinal use in Brazil.

Moraes *et al.* provided a review about the authenticity of plants marketed worldwide, using molecular methods including DNA barcoding and other molecular techniques [40].

The herbal medicine to be offered as an alternative to therapeutic supplement should be founded on the assurance of quality, effectiveness, and identity of the medicinal plant [28, 41].

Matos has reported that the best way to maintain the quality of medicinal plants and their preparations is to ensure a step of operations starting from planting, harvesting, preprocessing to the final product [42].

Several textbooks are addressing these aspects, and it is better to emphasize the National Program of Medicinal Plants and Herbal Medicines, and RDC18/2014 guidelines establishing good manufacturing and control practices within the Live Herbal Pharmacies of SUS [43].

The plant material through all these operational steps will be used as feedstock, which requires the qualified exercise of quality control in all these stages of the production chain of plant inputs [36].

Definitions and methodological operations of quality control for medicinal plants

Standards marketing

An important general aspect that determines the quality of the plant material is related to market conditions, especially for carrying out trade in inappropriate places exposing the product to improper conditions prone to contamination like extreme conditions of temperature and humidity [25].

A poor marketing condition of psychoactive herbal drugs in Diadema, São Paulo, Brazil has been reported by Soares Neto *et al.* and studies by Amaral *et al.* have demonstrated that the sale of medicinal plants in free markets and fairs in the city of São Luís, Maranhão, Brazil compromise the quality of products, emphasizing poor packaging plants, poor hygiene of food handlers, and garbage and sewage close to sale locations [44-46].

Still on the topic of the assessment of market conditions, being contacted that most of the plant material for medicinal purposes does not follow the current regulations determinations as evidenced by Soares and Mendonça [44].

Sampling

To perform the quality control of natural products, the prime step is to start with the sampling process, which must represent the whole lot, to be exercised in a specific location to avoid cross contamination, and in compliance with the provisions of literature [24,47].

Farias and Cardosoreported the sampling precautions that should be taken in the quality assessment of plant inputs, minimizing the risk of mistaken sample taken. The appropriate sampling supports the real results about the quality of plant materials, avoiding the wrong quality control report, not the characteristic of the plant but the analysis of a non-representative portion of the whole lot [48, 24].

Sensorial analysis

Traditionally, textbooks have presented parameters for assessing the quality of raw materials including the analysis of visual appearance, taste, odor and perception to the touch; and parameters may attest authenticity (identity) and purity [48].

The monographs of herbal drugs included in the Brazilian Pharmacopeia [47] define the sensory characteristics as a parameter for quality assessment. It can be considered that the determination of color, consistency, taste or odor is similar to the standard sample established in the literature for the drug in question, and it may be indicative of the plant drug identification. However, it's necessary to emphasize that it cannot be conclusive.

It is worth emphasizing that standard sample is one that is previously described in official textbooks such as the Brazilian Pharmacopoeia and assist in comparison with matter problem, either peel, leaf, and flower heads [47].

However, the analysis of these sensory characteristics can provide good indicators of quality, of the plant material such as signs of deterioration, (fig. 1), the color change by fungal contamination (fig. 2), the color change of plant samples desiccated indicating inadequate drying conditions, and perception of insects attack in the materials [48, 32].



Fig. 1: Signs of deterioration of commercial samples of *Peumus boldus* Molina (boldus) acquired in pharmacies from São Luís, Maranhão, Brazil



Fig. 2: Color change in commercial samples of *Vernonia polyanthes* Less (enxuga) sale in markets from São Luís, Maranhão, Brazil, showing fungal contamination

Authenticity of plant material in Brazil

According to Cardoso, authenticity can be defined as the act of comparing the botanical identity of the plant material to previously established standards, literature, pharmacopoeial monograph and pharmacognostic atlas [24].

The exchange of plant species may occur at various stages of the production chain, and it can be accidental or intentional, favored by the similarity between plant species and vernacular names [49].

For example, *Plectranthus barbatus* Andrews is a plant species with validation studies and included at the National List of plants of SUS interests [50]. It can be easily adulterated by *Plectranthus neochilus* Schltr and *Plectranthus grandis* (Cramer) R. Willemse.

All of them have morphological similarities, and they are known popularly as boldus, national boldo (boldo nacional), great boldo (boldo grande), skunk boldo (boldo-gambá), fake boldo (falso-boldo) among others [51, 42] (fig. 3).



Fig. 3: Details of leaves from *Plectranthus barbatus* Andrews (fake boldus), *Plectranthus neochilus* Schltr. (boldus) and *Plectranthus grandis* (Cramer) R. Willemse (great boldus)

Adulteration is considered an intentional substitution of a foreign plant, which increases the weight and consequently the profit. It is worth emphasizing that the adulteration by the substitution of another organ of the same plant, different from where the active ingredients are located and occurred in an intentional way is considered fraud [40]. It may result in loss of security because it can lead to severe poisoning or even death, due to the replacement of medicinal species by other toxic material [52].

Plant species *Echinodorus grandiflorus* and *Echinodorus macrophyllus*, known as "chapéu-de-couro," are indistinctly used as anti-inflammatory. Widely used with therapeutic purpose, it has been constantly suffered through the process of adulteration, mainly with floral parts indicating that the species were collected at the time of fruiting, or adulteration of the place where active ingredients should be located, the presence of plastic materials, living and dead insect's fragments, according to fig. 4 [53].



Fig. 4: Adulterations on samples from *Echinodorus grandiflorus* (Kunth) Micheli and *Echinodorus macrophyllus* (chapéu-de-couro). I. Flowers; II. Plastic materials; III. Insects [53]

Tobias *et al.* in their study of herbal medicines traded in drugstores of Maringá, Paraná, Brazil reported the problems of authenticity in herbal drugs from species widespread used in Brazil, for example, *Maytenus ilicifolia* (espinheira-santa), guarana (*Paullinia cupana* Kunth) and passion fruit (*Passiflora alata*) [54].

The authenticity of plant material has been evaluated by macroscopic and microscopic tests, based on comparison with an authentic standard sample, descriptions in Pharmacopoeias or literature. Microscopic examination [33] can be based on the research of specific structures like epidermal features (trichomes and stomatas), glandular elements, crystals, vessels, fibers, starch, among others. It may be still held the histochemical reactions [46]. The authenticity can also be evaluated by the presence of active chemical constituents of the species called chemical markers [45, 55, 24].

Studies conducted by Donato and Morretes with *Myrcia multiflora* (Lam.) DC. (pedra-ume-cá) (Myrtaceae family) and by Padilha *et al.* with *Morus nigra* L. (blackberry, Moraceae family), emphasized the

representation of macro and microscopic tests on the verification of authenticity of these species [56, 57]. The morphological and anatomical studies of medicinal plants are essential to support the evaluation process of authenticity and are provided by several studies [58]. The Brazilian Pharmacopoeia in its various editions also represents an important source of comparison for quality evaluation.

Milaneze-Gutierrez *et al.* in their study for evaluating the authenticity of *Plectranthus barbatus* and *Plectranthus grandis* samples, demonstrated that the leaves of both species are morphologically similar, making it difficult to differentiate by macroscopic characteristics. But the anatomical analysis, quantity of glandular and non-glandular trichomes allowed the differentiation of two species of *Plectranthus* both in fresh samples and dried fragments [51]. It is necessary here to point out that the phytochemical profile which allows us to identify the presence of a group of substances that may help in identifying the plant sample in a simple, fast and economical way [59].

The RDC 26/2014, the legislation that regulates the herbal medicine registration in Brazil, establishes the marker concept as a "substance or class of substances (ex: alkaloids, flavonoids, fatty acids, etc.) present in the raw material which is used as a reference in quality control of raw plant material and herbal medicine". According to this legislation, the marker preferably should have a correlation with therapeutic effect. However, it also can be just an analytical marker, when its relationship with the therapeutic activity has not been proved so far [18].

Engel *et al.* evaluated the authenticity of commercial samples of *Bauhinia forficata* Link (pata de vaca). Adulterations in the samples were found based on chromatographic profiles, identifying the flavonoid kaempferitrin, which is the analytical chemical marker for this species [60].

Mikania glomerata Spreng and *Mikania laevigata* Schultz Bip. ex Baker are species widely used by the population for treatment of respiratory diseases and are common known as guaco [61]. Both of these species have morphoanatomical similarities, and they are sold without distinction due to limited differentiation by macro and microscopic tests. These species have as the chemical marker, coumarin (1,2-benzopyrone) however, it is also hard to differentiate them based on their chemical marker [62].

Bolina, Garcia, and Duarte reported the presence of coumarin, triterpenes, steroids and glycosylated flavonoids in both *Mikania glomerata* Spreng and *Mikania laevigata* Schultz Bip. ex Baker, showing similar chemical profile which it is not appropriated to the differentiation of those species [63].

These studies are examples that assessment of authenticity based on the definition of the analytical marker is not always effective. The presence of substances may be common to several plant species, mainly from the same family or genera. Therefore, it cannot be used as a sole method of identification [64].

In addition to the difficulty to evaluate the authenticity of plant samples with similar morpho-anatomical characteristics and chemical markers, the analysis may be impaired when the material is fragmented, mainly powdered. Usually, this situation prevails in the commercialization, making the macro and microscopic analysis more difficult. Concerning chemical testing, we must remember that many edaphic-climatic factors of planting and gathering place, and inadequate conditions of drying or storage can cause alteration of the chemical composition thus making it difficult to identify based on these tests [64, 25, 40].

In real prospect of overcoming the difficulties of those usual methods for evaluating the authenticity, molecular biology has been used, with excellent possibilities of success, proven by studies in the area which have already been published. Although it is considered the most efficient method to test the authenticity of plants, it hasn't been described in the quality control evaluation guides of preparations with plants yet, published by WHO, nor in the laws of countries where there's regulation of herbal medicine or dietary supplements [40]. Only the Chinese Pharmacopoeia (Pharmacopoeia of the People's Republic of China) presents molecular biology methods described for plant authenticity of analysis used in traditional Chinese medicine [65, 66, 40].

Among the methods to study the DNA for plant identification, DNA Barcoding has been proved to be the most reliable method to check the authenticity of raw plant material due to its accuracy, speed, reproducibility, and relative simplicity [33]. It was developed in 2003 for the identification of animals by using the mitochondrial COX1 gene. Later, this method was also used to identify higher plant species. However, for this propose, it was necessary to add other genes and intergenic regions of the mitochondrial, nuclear or chloroplast DNA as *rbcl*, *matK*, 18S, 5.8S, ITS 1, ITS 2, *trnH-psbA*, among others [67-70].

Studies by Moraes *et al.* showed that although there is reliability in the identification and relative simplicity in its use, there are difficulties in this procedure, primarily related to the cost of these techniques. Accordingly, molecular methods should only be employed when conventional techniques are not effective in evaluating authenticity [40].

Purity of plant material

The quality control is based on the evaluation of purity, which is related to detection of foreign organic or inorganic elements (endogenous and exogenous), moisture content, microbial contamination, parasitic, pesticide residues, heavy metals [24].

According to RDC 26/2014, the plant raw material must present purity report, including foreign matter, water content, total ashes content, and ash insoluble acid. This evaluation also includes the determination of heavy metals, residues of pesticides radioactivity, when applicable, microbiological contaminants and mycotoxins [20]. The tolerance limits are expressed numerically for a maximum and minimum value of each foreign material and are presented in the literature. It indicates the purity of the plant material, and usually, it is expressed in percentage or absolute terms [47, 36].

According to the last version of Brazilian Pharmacopoeia "plant drugs should be free from fungi, insects, bacteria and other contamination". Unless otherwise indicated, the percentage of foreign elements should not exceed 2% w/w [47].

The analysis of foreign elements can be performed macroscopically (whole or grounded plant) [24]. According to the Brazilian Pharmacopoeia, foreign matters are classified into three types: (a) parts of the plant from which the drugs are derived (b) any parts or products of other organisms than those specified in the definition and description of the drug in their respective monograph, and (c) other impurities, minerals or organic, non-related to the drug [47].

A study by Lucca *et al.* about purity evaluation of fifteen (15) commercial samples of chamomile (*Chamomilla recutita* L.), that represents the widely used drug in the popular practice in Brazil, showed that although all samples were authentic, six (06) samples had foreign matter content above 5% [71]. These materials included the living and dead insects; which can be related to the crop and inappropriate post-harvest transport, as well as lack of quality control before and after the packaging operation. In this study, they also found other parts of the chamomile different than the place where active ingredients are located (flowers). (fig. 5) [24].



Fig. 5: The strange material in commercial samples of dry leaves from *Peumus boldus* Molina (boldus), acquired in popular markets in São Luís, Maranhão, Brazil

Lopes and Netto Junior studied the quality control of commercial samples of guarana (*Paullinia cupana* Kunth), found strange materials present at a level above its threshold value (9.5%), proving the poor quality of the samples [72].

The excessive presence of water in crude drugs allows the action of enzymes, which can promote chemical degradation of the constituents. In additional, the high amount of water can also promote the growth of microorganisms such as bacteria and fungi. According to the Brazilian Pharmacopoeia, the moisture content limit varies from 8% to 14% according to the species and part of the plant [47].

Quality assessment study of herbal drugs commercialized in drugstores of Maringá, PR, Brazil showed that among the ninety-two

(92) samples analyzed, 15.4% were rejected because they presented levels of the content of total and acid insoluble ashes that were above the permissible limits [54].

The determination of the ashes content allows verification of non-volatile inorganic impurities, indicating the presence of contaminants such as soil or sand [48]. Ash content outside the standards can also report problems in authenticity as an exchange of plant species or a mixture of different species [37].

A study of Schwanz addressed to the risks and hazards associated with the presence of heavy metals in medicinal plants showed the warning that the plants can easily absorb metals present in the environment. This contamination causes accumulation of these elements in plant tissues, representing the risks associated with metals phytotoxicity, and toxicity to human and animal health [73].

Farias showed that the contamination by heavy metals in pharmaceutical products is related to the presence of lead, arsenic, cadmium, copper and mercury, as well as the presence of pesticides. It is important to emphasize that pesticides are elements whose intake should be restricted given the proven toxic effects [48].

Soares Neto *et al.* evaluated the contamination by pathogenic microorganisms in samples of psychoactive herbal drugs, acquired in the popular trading of Diadema, São Paulo, Brazil. They found that 66.7% of samples did not conform to the quality specifications, being evidenced heterotrophic bacteria, fungi, and/or enterobacteria above the established limits [52].

The contamination of plant products through pathogenic microorganisms should be related to inadequate conditions of harvest and post-harvest processing [74]. According to Matos and Oliveira and Akisue, contamination of herbal drugs by fungi, besides representing risk due to the production of toxic substances (mycotoxins), can lead to the destruction and/or alteration of active ingredients, making them unfit for consumption, regardless of the level of contamination [37, 55, 59].

The research of undesirable chemical constituents in the test sample can be used as criteria for purity evaluation. Thus, the finding of mycotoxins, such as aflatoxin in plant sample shows poor quality of the material, the same manner as the verification of the presence of a substance of secondary metabolism that is not synthesized by the plant [48].

Integrity of plant material

The integrity evaluation is based on qualitative and quantitative assays, being indispensable in quality control. It is important to considerate that plant raw materials may exhibit variability in chemical composition, depending on several intrinsic and extrinsic [38] factors, influencing the concentration of chemical constituents in plant material, and therefore in the therapeutic value of the herbal products [66].

Klein emphasized that botanical may be as effective as medicines obtained from chemical synthesis since the operations of plant transformations in a medicine prioritize the preservation of the chemical integrity of active principles, and hence, the pharmacological action of the plant, ensuring the constancy of the desired biological action [1].

As usual, a methodology for the initial study of integrity, Matos established the methodology that can be used for screening tests or phytochemical screening. These tests identify the classes of secondary metabolites by specific reactions and are very helpful due to its speed, efficiency, and low cost [9, 59].

However, the phytochemical screening is limited, since it signals just the presence of secondary metabolites classes. Thus, for the identification of specific markers, it is necessary to do further studies with isolation and structural elucidation of the active ingredients or substances responsible for the biological action (active marker), using chemical, physical methods or physicochemical involving characterization techniques, chromatographic methods, mass spectrometry, ultraviolet

spectroscopy, (visible and infrared) as well as proton and carbon nuclear magnetic resonance (NMR) [75, 59, 38].

As mentioned earlier, the RDC 26/2014 which regulates the registration and notification of industrialized herbal, brings a definition of markers (analytical or active), previously named chemical marker. It is necessary to emphasize that the defining the analytical marker is not an easy task, considering that when we speak of the effectiveness of plant drugs and derivatives products we are referring to synergistic action Phyto-complex, not only isolated substance [20].

The official compendia, particularly in Brazil, as the Brazilian Pharmacopoeia defines the chromatographic methods such as thin layer, liquid high-resolution and gas chromatography. Hence, there are several studies based on chromatography, being directly linked to the quality control of commercial samples of herbal drugs and derived preparations widely used for therapeutic purposes [47].

We can cite same studies developed based on research markers by chromatographic methods such as the presence of derivatives of o-hydroxycinnamic acid in *Echinodorus grandiflorus* (Cham and Schltdl.); coumarin in species *Mikania glomerata* Spreng [61] and *Mikania laevigata* Sch. Bip. ex Baker; kaempferitrin in *Bauhinia forficata* Link [60]; aescinia from *Aesculus hippocastanum* L [76], and flavonoids in *Ginkgo biloba* L [27].

According to Migliato *et al.* standardization studies should prioritize the evaluation of plant extracts through factorial design, emphasizing the definition of variables that influence the extraction, since this is a crucial step in getting herbal substance, ensuring the separation substances of interest from complex matrix [77].

CONCLUSION

The above literature shows the importance of studies to evaluate the quality of products obtained from plants that are commercialized in the formal and informal trade across the Brazilian territory in order to guarantee the security of the population that uses these products. From this review conducted on quality control plant raw materials, it is possible to observe quality issues, mainly regarding the authenticity and purity of materials, emphasizing the potential problems of poisoning that can occur from the consumption of products based on plants with poor quality.

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CONFLICT OF INTERESTS

Declared none

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