Medicinal Plants and Herbal Products From Brazil: How Can We Improve Quality?

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Keywords: Brazil, conservation, metabarcoding, resilient plants, traditional knowledge

INTRODUCTION

Brazil has widely diverse flora, rich in medicinal plants, which are an important part of the Amerindian traditional knowledge (Levis et al., 2017). Some Brazilian plants were included decades ago in different Pharmacopoeias because they provide important substances used in medical practice worldwide. Examples are Carapichea ipecacuanha (Brot.) L. Andersson (ipecac), source of the emetic and amoebicide alkaloid emetine, and Pilocarpus microphyllus Stap ex Wardlaw, source of the antiglaucoma pilocarpine (Nogueira et al., 2010). More recently, Açaí (Euterpe oleracea Mart.), native from the Amazon rainforest, became notorious in the international market as a nutraceutical (Carey et al., 2017). Despite its potential, the native vegetation of Brazil has been undergoing intense destruction: all the ecosystems, including the Amazon rainforest, have been quickly replaced by monocultures of sugarcane, soybeans, eucalyptus, and livestock, leading to an intense process of genetic and cultural erosion. On the other side, more recently, the development of bioproducts from Brazilian plants has been stimulated, aiming at a market based in the bioeconomy, which not only brings health benefits but also is important for conservation of biodiversity and consequent mitigation of climate changes (Dinerstein et al., 2020). However, due to the current precarious situation of the herbal products market in Brazil, many steps need to be taken until such a goal is achieved.

QUALITY OF HERBAL PRODUCTS FROM BRAZIL

The denomination herbal products (HP), in Brazil, includes dried plants, sold as tea, and also the finished products used as medicine, nutraceutical, or cosmetics. In this internal market, it is possible to find HP from plant species from three different origins: i) native species that are collected in the local ecosystems, ii) cultivated exotic species, and iii) imported species (mainly dry plants and extracts). HP from i) are mainly commercialized in local markets while HP from ii) and iii) can be found in pharmacies and natural products shops. Since the 1960s, there are regulatory rules for the correct identification of medicinal plants for the commerce in Brazil (Brasil 1967), and more recently, new legislation was launched for regulating the commerce of plants used in traditional knowledge (Carvalho et al., 2018). Despite such efforts, studies done using classical analytical procedures, provided by monographs from Brazilian Pharmacopoeia and Pharmacopoeia from other countries, have shown the existence of serious problems.

Studies with species from the group i) uncovered different problems. Contamination with potentially pathogenic bacteria (enterobacteria and other Gram-negative bacteria) and fungi...
(Aspergillus spp. and Penicillium spp.) was found in samples of Brazilian ginseng (P. glomerata (Spreng.) Pedersen and P. paniculata Mart.) (Zaroni et al., 2004) and “mate” (Ilex paraguariensis A.St.-Hil.) (Borges et al., 2002). Adulteration in leaves of “guaco” (Mikania glomerata Spreng. and M. laevigata Sch. Bip. ex Bak) was detected in different studies that have shown species substitution and presence of other parts of the plant, insects, and sand (Alvarenga et al., 2009; Melo and Sawaya 2015; Palhares et al., 2015). Samples of “guaraná” (Paullinia cupana Kunth) presented low levels of methylxanthines and presence of inorganic materials (sand and earth) and nonessential metals (Araújo et al., 2006; Bara et al., 2006; Sousa et al., 2011). Parts of insects and nonessential minerals were also found in samples of “carqueja” (Baccharis crispa Spreng) (Ferrante et al., 2007), “pata-de-vaca” (Bauhinia forficata Link) (Engel et al., 2008), and “espinheira-santa” (Maytenus ilicifolia Mart. ex Reissek, syn. Monteverdia ilicifolia (Mart. ex Reissek) Biral) (Leal et al., 2013). Our group also showed that, from a total of 252 samples of native plants with historical use in Brazilian traditional medicine, purchased from popular markets in all the regions of Brazil, only 50.2% corresponded to the original species (Brandão et al., 2013). It is important to note that P. glomerata, P. paniculata, I. paraguariensis, M. glomerata, M. laevigata, P. cupana, B. crispa, B. forficata, and M. ilicifolia are also commercialized in other countries, suggesting that the problems found in the Brazilian market may be present in the international market as well.

More recently, we added DNA barcoding techniques to the classical analytical studies. One of our studies showed that samples of barks of the Brazilian quina (Remijia ferruginea (A.St.-Hil.) DC. and Strychnos pseudquina A. St.-Hil.) were substituted by other species without any correlation to traditional medicine (Palhares et al., 2014). In a similar study, we have analyzed 257 commercial samples of the native species i) M. ilicifolia and Mikania spp. as well as exotic species ii) Matricaria recutita L. and Passiflora incarnata L. and imported species iii) Hamamelis virginiana L., Panax ginseng C. A. Mey, Peumus boldus Molina, and Valeriana officinalis L. This study showed that substitutions may be as high as 71% (Palhares et al., 2015). In a recent review, Ichim (2019) also showed the results of studies using DNA-based methods for species identification in herbal products commercialized in 37 countries. In Brazil, besides our results (Palhares et al., 2015), the author showed that a study using DNA barcode and a wider range of markers (ITS, trnl, trnL-trnF, psbA-trnH, matK, and rbcL) evidenced substitutions in “quebra-pedra” (Phyllanthus spp.) (Inglis et al., 2018). In another study done also with M. ilicifolia using PCR-RFLP technique, substitution was also an issue (Nakamura et al., 2013). On the other hand, when analyzing the complete ITS/5.8S region in commercial samples of “Brazilian arnica” (Egletes viscasa (L) Less), no substitutions were found (Batista et al., 2012). In his review, Ichim concludes that the highest percentage of adulterated commercial HPs among all countries was reported for Brazil.

In another review, Ichim et al. (2020) show results of studies on authenticity using microscopic analysis on 508 herbal medicines and food supplements traded in thirteen countries or territories. All or at least most (>70%) herbal products were reported to be authentic in Argentina, China, Germany, Thailand, and Egypt. In the United States and Peru, a substantial part (>30%) was wrongly declared, and a third group of countries, comprising Iran, Brazil, India, Turkey, and Greece, showed authenticity score lower than 40%. Overall, almost half (49%) of the total products (n = 167) microscopically authenticated in Asia were reported to be adulterated, followed by South America (40%) and Europe (39%) and more distantly by North America (33%). Other studies also show that very known and used medicinal plants marketed in Europe, Asia, and the United States such as Hypericum perforatum L. (Raclariu et al., 2017), Echinacea spp. (Raclariu et al., 2018), and M. recutita (Guzelmeric et al., 2017) are often adulterated or show low quality. Other problems were described for Ayurvedic herbal products sold in Norway, Romania, and Sweden (Seethapathy et al., 2019), HP sold in Canada and United States (Newmaster et al., 2013), and Traditional Chinese Medicines (TCM) entering the Australian market (Coghlan et al., 2012), among other countries.

**DISCUSSION**

Considering the current situation of the HP sold in Brazil, some points must be considered to reach the full potential and benefits from it:

1. Develop Pharmacopoeia Monographs for Brazilian native plants including DNA barcode. In the last years, DNA barcoding from different organisms has gained rapid acceptance in the scientific community from various fields, including studies of plant identification (CBOL Plant Working Group, 2009). Despite DNA barcoding being relatively new, pharmacopoeias around the world, such as Ayurveda (Indian), British, Chinese, and Korean, have already introduced protocols for DNA barcoding authentication. In the last decade, significant advances regarding DNA sequencing were made, making this technique more viable to be used for the purpose of species identification in complex samples. Herbal products may contain several species in their composition, and even when the product is declared to contain only one species, we may encounter adulteration by the addition of other species. The methodological advances in high-throughput sequencing (HTS) were crucial to the analysis of those samples. Different from Sanger sequencing, which has the limitation of only analyzing one sample per reaction, HTS made the parallel sequencing of thousands of samples possible simultaneously in a cost-effective manner, besides being more sensitive and faster (Coghlan et al., 2012; Ivanova et al., 2016). Combining the use of DNA barcoding and HTS, the metabarcoding technique was developed. Metabarcoding is the use of universal PCR primers to mass-amplify barcodes from DNA extracted from complex samples (de Boer et al., 2015). This technique has been used more and more, allowing the study of thousands of samples of HPs simultaneously to evaluate their authenticity and safety (Ivanova et al., 2016; Seethapathy et al., 2019; Urumarudappa et al., 2020). Despite its benefits, DNA...
It is imperative to respect the regulations to protect the Brazilian biodiversity. Ichim (2019) showed that adulteration in HP marketed in Asia and Africa is less common than in other countries. This occurs because in these continents traditional medicines are strongly recognized by population. Since 2014, our research group is also doing a set of works with school teachers and students living in small cities, showing them the importance of plant biodiversity and traditional knowledge associated with them (Prates et al., 2020). It is strongly necessary to promote such activities in all regions of Brazil; nobody protects or values what they do not know!

CONCLUSION

The adulteration found in Brazilian HP reflects a trend that can be seen throughout the world. The points listed can contribute to improving their quality, especially those from native Brazilian species.

AUTHOR CONTRIBUTIONS

All authors contributed to the bibliographic survey and preparation of the manuscript, each writing about their area of knowledge. MGLB was also responsible for coordinating the group and funding acquisition.

FUNDING

The study was funded by Fundação de Apoio a Pesquisa do Estado de Minas Gerais (FAPEMIG/PPM00691-16) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPQ/310389/2017-8).

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