

## Pharmaceutical Care in Phytotherapy: quality of *Passiflora* spp. products purchased from pharmacies in São Luís, Maranhão, Brazil

### Atenção Farmacêutica em Fitoterapia: qualidade de produtos de *Passiflora* spp. adquiridos em farmácias de São Luís, Maranhão, Brasil

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#### ABSTRACT

The use of plants and their products as a therapeutic resource is expanding, reflecting the tendency to use natural products of plant origin in the recovery of health, a worrying situation, considering the risks associated with the use of poor-quality products for medicinal purposes. Thus, this study proposes to evaluate the quality samples of leaves of *Passiflora* spp., used for medicinal use by the Maranhão population, sold in São Luís, Maranhão, Brazil. Samples acquired in five pharmaceutical establishments were submitted to quality assessment using marketing parameters, authenticity, integrity, and purity. Most samples do not meet legal labeling parameters and there is wide price variation. All samples are within the limits of the specialized literature regarding water content, foam content, and total ash. In the quantification of flavonoids, two samples presented values lower than that required by the official monograph. The results show the need for greater supervision, surveillance, and quality control of medicinal plant material made available for commercialization.

**Keywords:** *Passiflora*; Authenticity; Purity; Integrity; Pharmacovigilance.

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#### RESUMO

A utilização de plantas e seus produtos como recurso terapêutico encontra-se em expansão, refletindo a tendência em utilizar produtos naturais de origem vegetal na recuperação da saúde, situação preocupante, considerando os riscos associados à utilização de produtos de má qualidade para fins medicinais. Assim, esse estudo propõe avaliar a qualidade amostras de folhas de *Passiflora* spp., empregadas para uso medicinal pela população maranhense, comercializadas em São Luís, Maranhão, Brasil. Amostras adquiridas em cinco estabelecimentos farmacêuticos foram submetidas à avaliação de qualidade utilizando parâmetros de comercialização, autenticidade, integridade e pureza. A maioria das amostras não atende aos parâmetros legais de rotulagem e há grande variação de preço. Todas as amostras estão dentro dos limites da literatura especializada em relação ao teor de água, índice de espuma e cinzas totais. Na quantificação de flavonoides, duas amostras apresentaram valores inferiores ao exigido pela monografia oficial. Os resultados evidenciam necessidade de maior fiscalização, vigilância e controle de qualidade do material vegetal medicinal disponibilizado para comercialização.

**Palavras-chave:** *Passiflora*; Autenticidade; Pureza; Integridade; Farmacovigilância.

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## INTRODUCTION

Plants used for medicinal purposes, whether as a traditional practice or as an alternative and complementary allopathy has its benefits recognized and stated by the World Health Organization (WHO), however, it should be ensured it is offered in a safe, effective, efficient, qualified and rational way since 85% of the world population use these plants and/or their derivatives in primary health care (BRAZIL, 2012; AMARAL et al., 2021).

Among the main factors responsible for the increasing use of medicinal plants and herbal medicines are the failure and side effects of traditional pharmacological treatments, especially because of the misuse or abuse of these medicines. Added to this, the inaccessibility of a large part of the world's population to basic health services, and the popular belief that the use of plants is not dangerous. “If it is natural, it does not hurt” (LEAL; TELLIS, 2015; OLIVEIRA et al., 2018).

The intense spread of Phytotherapy in the last few years combined with the need to guarantee the use of qualified products caused in Brazil the publication of many normative determinations with emphasis on the National Policy of Medicinal Plants and Phytotherapics (BRAZIL, 2006a) and the National Policy of Complementary and Integrative Unified Health System (BRAZIL, 2006b).

Despite the current normative determinations, a national study conducted in several regions of Brazil showed that products marketed in the national market as herbal medicines present problems of poor quality regarding the aspects of authenticity, purity, and integrity of plant raw materials, representing a real risk to consumers (DIAS et al., 2013; BRITO et al., 2016).

In the face of this reality, the Brazilian National Health Surveillance Agency published Resolution no. 26/14, which establishes the quality parameters for the registration and notification of herbal medicine and traditional herbal product, with emphasis on physical-chemical, chemical, and microbiological quality control (BRAZIL, 2014).

It is worth mentioning that in the real perspective of providing quality plant products, chemical standardization studies should be developed, with the definition of active and/or analytical markers to guarantee efficacy and safety (BRAZIL, 2014); as well as the search for contamination by bacteria and fungi, which may result in the destruction and/or alteration of the active principles and/or cause the production of toxic substances,

such as aflatoxins, mycotoxins produced by various species of fungi and proven to be contaminated plant products for medicinal purposes (BRITO et al., 2016).

Studies have found that among the native plant species commonly used for medicinal purposes by the Brazilian population, the species of the genus *Passiflora* has been highlighted (AGRA et al., 2008; NEIVA et al., 2014) with broad and diverse therapeutic popular use; easily available for sale in pharmaceutical, naturist and informal trade (ZERAİK et al., 2010).

The genus *Passiflora* is the largest in the family Passifloraceae, with about 400 species, all of which are to be found in Brazil is known popularly as passion fruit and used commonly as anti-anxiety medications, sedatives, diuretics, and analgesics (BERALDO; KATO, 2010).

*Passiflora edulis* Sims and *Passiflora alata* Curtis included in Brazilian Pharmacopoeia (BRAZIL, 2019) and in the National List of Medicinal Plants of Interest to the Unified Health System (RENISUS) (BRAZIL, 2009) represent the most traded *Passiflora* species in Brazil. Despite the botanical similarities, studies show that there are differences in the identification and quantification of its chemical constituents, mainly flavonoids, capable of causing different biological responses (MÜLLER, 2005).

Thus, this study proposes to evaluate the quality of commercial samples purchased as passion fruit in pharmaceutical establishments in the city of São Luís, Maranhão, Brazil, aiming at an effective contribution to Pharmacovigilance in Phytotherapy.

## **METHOD**

Considering that *Passiflora alata* or *Passiflora edulis* species are marketed as vegetal drugs or dry extract, under the name of passion fruit, in some methodological steps of this study commercial samples acquired for analysis were subjected to specific methodologies to evaluate quality parameters (authenticity, purity, and integrity) described in the literature for each of these species and/or their pharmaceutical forms.

### **Acquisition of plant material**

Based on the register of pharmaceutical establishments of the Regional Council of Pharmacy of Maranhão and the Sanitary Surveillance Superintendence of São Luís, the pharmaceutical establishments with trade-in vegetal drug and/or preparations derived from leaves of *Passiflora* spp. in the 05 (five) most populous neighborhoods of the capital: Centro (A), COHAB (B), Renascença (C); Monte Castelo (D) and COHAMA (E).

The samples marketed as passion fruit were obtained by purchase, packed separately, in sterile plastic bags, identified by codes, and kept in appropriate conditions for the analysis. Information on the price, condition, packaging and labeling of each sample acquired was analyzed according to provisions in current regulations (BRAZIL, 2013).

### **Evaluation of authenticity, integrity, and purity of the vegetal drug and derived preparations marketed as passion fruit**

From each of the samples taken representative aliquots were for analysis by direct unarmed identification processes. The color characteristics, size, weight, signs of deterioration, and presence of foreign material were found in making research (CARDOSO, 2009; BRAZIL, 2019).

Comparative microscopic techniques were applied (BRAZIL, 2019). Samples purchased as a dry extract were analyzed by stereomicroscope for the identification of undeclared plant tissues and/or excipients (APARECIDO-GOUVEIA et al., 2022).

It was carried out the survey of the bacteria from uniform aliquot seeding of samples in a broth study of Brain Heart Infusion (BHI) and on MacConkey agar plates where three aliquots were seeded at different points, with incubation at 37 °C for 24 to 48 hours and observed bacterial growth (WHO, 1998).

Vegetal drug samples were subjected to water determination by gravimetric method, total ash, and foam index (BRAZIL, 2019). For the quantification of flavonoids, were applied the spectrophotometric methods described in official compendia for analysis of *Passiflora* species in the form of vegetal drugs (BRAZIL, 2019), *Passiflora incarnata* dry extract (FRENCH PHARMACOPOEIA, 1992) and *Passiflora alata* dry extract were used (PETRY et al., 1998).

The tests were performed in triplicate and the results were expressed as mean  $\pm$  standard deviation and submitted to analysis of variance (ANOVA) and Tukey's multiple comparisons test to determine significant differences between the means, considering a significance level of  $p < 0,05$ . Data were analyzed using *GraphPad Prism 5.0* (2007), software from GraphPad Software.

## **RESULTS AND DISCUSSION**

In the 05 (five) most populous neighborhoods of São Luís, were identified 05 (five) pharmaceutical establishments (A - E) that traded products with passion fruit leaves; was observed that each establishment had only 01 (one) supplier of the product.

Among the acquired samples (1 - 5), 03 (three) were verbally identified by the responsible pharmacist as *Passiflora incarnata*, 01 (one) as *Passiflora alata*, and another only as *Passiflora*. These samples were available in the form of dry extract capsules, vegetable drug capsules, and also vegetable drug sachets (Table 1).

**Table 1.** Description of commercial samples of *Passiflora* purchased from pharmaceutical establishments in São Luís, Maranhão, Brazil neighborhoods.

Neighborhood	PE <sup>a</sup>	Provider	Presentation form	Referenced botanical nomenclature <sup>b</sup>	Code
Centro	A	1	Dry extract in capsules	<i>Passiflora incarnata</i> L.	1
COHAB	B	1	Dry extract in capsules	<i>Passiflora incarnata</i> L.	2
Renascença	C	1	Dry extract in capsules	<i>Passiflora alata</i> Curtis	3
Monte Castelo	D	1	Vegetable drug in capsules	<i>Passiflora</i> spp.	4
COHAMA	E	1	Vegetable drug in sachet	<i>Passiflora incarnata</i> L.	5

<sup>a</sup>EF: pharmaceutical establishment; <sup>b</sup> Information obtained from a responsible pharmacist.

The majority (60%) of the samples purchased were identified as *Passiflora incarnata*, which is one of the most studied species and is found in commerce, being registered in the European Pharmacopoeia (2000) and is referred to as the synonymy of the *Passiflora edulis* according to collections such as *The Plant List* and in the *Tropics*. As a result, the standards set forth in the literature and compendium of the species referred to as *Passiflora edulis* shall be applied in the evaluation of the quality of the samples that they have acquired as *Passiflora incarnata*.

It should be noted that, in the Brazilian Pharmacopoeia Herbal Medicines Form, the genus, *Passiflora* is enrolled (*Passiflora alata* Curtis, *Passiflora edulis* Sims and *Passiflora incarnata* L.), however, as already pointed out, *Passiflora edulis* and *Passiflora incarnata* are synonyms, therefore refer to the same species; what deserves a review of this information from Herbal Medicines Form.

In this study, it was shown that, in spite of the wide range of drugs, plants, and/or preparations derived from the leaves of *Passiflora* spp. in the main districts of the city, there is little diversification regarding the way they are presented, prevailed a presentation in the form of a dry extract and in the drug. It is worth emphasizing that changes in the pharmaceutical form lead to a differentiation in the timing and dosage of the preparations,

which will require attention at the time of the pharmaceutical orientation (EFFERTH; KAINA, 2011).

Price analysis among the commercial samples purchased revealed similarity between establishments offering products in the form of dry extract capsules (1, 2, and 3); noting that they were superior to the samples to be marketed as a vegetal drug (4 e 5). However, it was found that among the drug samples there was a high price difference, evidencing that the drug in capsule form (4) was offered with a value approximately five times higher than the drug in sachet (5).

The price differences between similar plant samples may be justified by manufacturers' spending on the pharmaceutical technology process used and the type of packaging, but it also may be related to the quality of the products that are being offered, whether in the raw material or the finished product (CARVALHO et al., 2010).

The samples of passion fruit samples in capsules, whether as a dry extract or as a vegetal drug, were stored in a rigid plastic container with a lid, sealed, and labeled. Only the vegetal drug sample (5) was packaged in a tightly sealed, labeled plastic sachet.

In the analysis of the identification of the samples, it was found that it was made exclusively by the label on the package; and it is clear that samples 2, 3, and 4, were identified by the following nomenclature popular plant species (passion fruit), while that of sample 1 by the genus (*Passiflora*) and only sample 5 had complete drug binomial (*Passiflora incarnata*).

According to Resolution no. 67/2007, in the labeling of magisterial preparations, the substance that makes up all of the same is to be written according to the common name in Brazil (BRAZIL, 2007), and thus, in the case of the plant species in this study, the *Passiflora alata* Curtis and *Passiflora incarnata* L., none of the samples met this requirement.

The sample of a vegetable drug in sachet (5) is exempt from registration according to Resolution no. 27/2010 (BRAZIL, 2010); being marketed in the tea category, which also dispenses with mandatory nutrition labeling. We must emphasize that the packaging and the label, besides fulfilling the function of making direct contact between the product and the user, have aesthetic, technical, and informative functions; therefore, they must comply with current legislation to contribute to the effective and safe use of the drug; being indispensable to comply with these standards aiming at the quality of treatment

offered to the patient, while wrong and/or incorrect information leads to the incorrect use of the drug.

In the sensory analysis, it was found that not all commercial samples of passion fruit in the form of a dry extract (samples 1, 2, and 3) or in the form of drug-plant samples 4 and 5) produced uniformity of color.

The change in the color of the samples may be justified by the variation in methods of obtaining final products, such as the drying and extraction method. Changes in the coloration of the sample plants dried may be indicative of an improper drying process, occurring photodecomposition, which can lead to the degradation of the chemical components and the integrity of the piece (CARVALHO et al., 2010). In addition to this, the different colors of the extracts from plants of the same species may be related to the different substances that are extracted, as a function of the acidity or alkalinity of the medium (SIMÕES et al., 2017).

Capsule samples (1 e 4) were characterized as fine dust particles; only sample 5 presented particles classified as coarse dust and the presence of foreign material, with an index of 76.3%, predominating branches and stones. Disturbing information, since the maximum allowed by the official monograph of the species, is 2% (BRAZIL, 2019). None of the samples showed signs of deterioration.

In the analysis of the average weight of the capsules (1 e 4), it was noted that only sample 4 showed an average weight lower than that indicated on the product label, while the others were in agreement, as specified on the packaging and the variation of the weight to the maximum extent permitted by Brazilian Pharmacopoeia (BRAZIL, 2019) (Table 2). The sample of the vegetal drug acquired in a package of 50 grams of the presented material has a weight corresponding to the indicated.

**Table 2.** Weight (average and labeled) of samples of commercial *Passiflora* capsules purchased from pharmaceutical establishments in São Luís, Maranhão, Brazil neighborhoods.

Sample	Average Weight (g)	Labeled Weight (g)
1	0.491 ± 0.012	0.5
2	0.550 ± 0.013	0.5
3	0.275 ± 0.011	0.3
4	0.279 ± 0.008	0.5

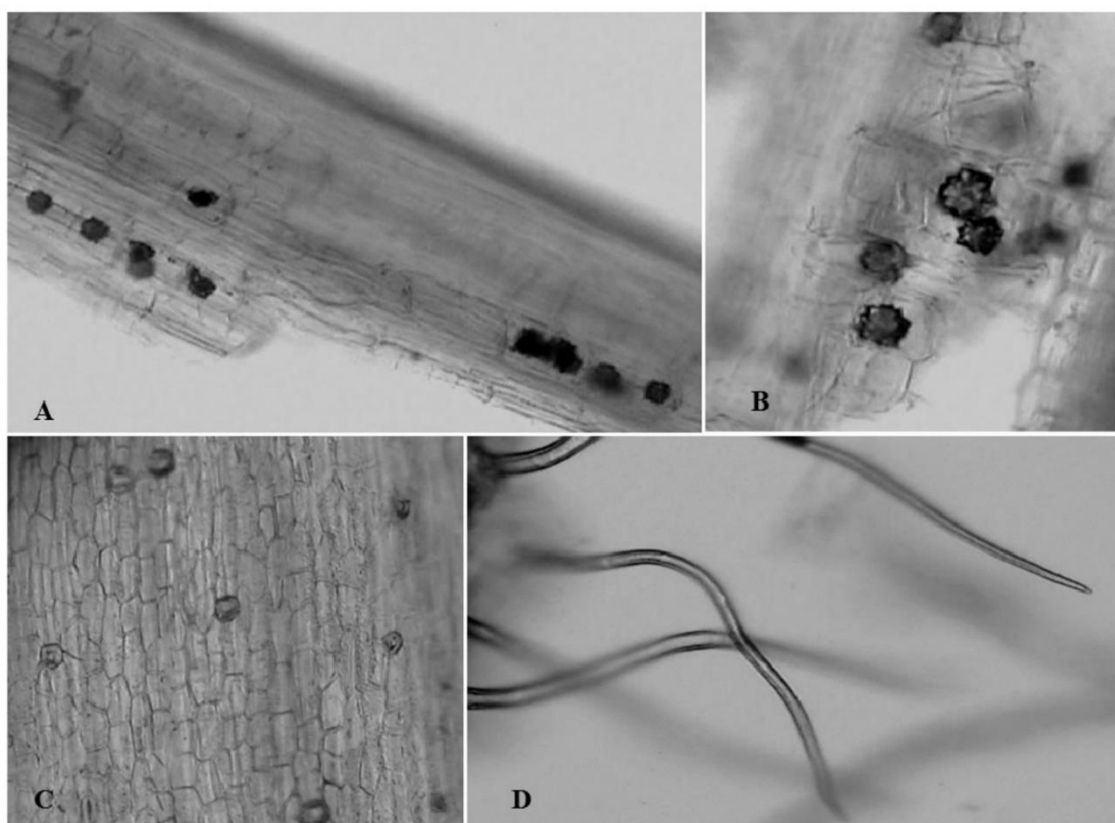
The standardization of the average weight aims to allow the administration of the precise and effective dose of the active component used in therapy, as well as ensure the



safe use of the medicine and adapting it in specific cases. When these values are outside the specified standard, there may occur failure and/or adverse effects resulting in insufficient administration or excess beyond safe limits (BOTH et al., 2015; APARECIDO-GOUVEIA et al., 2022).

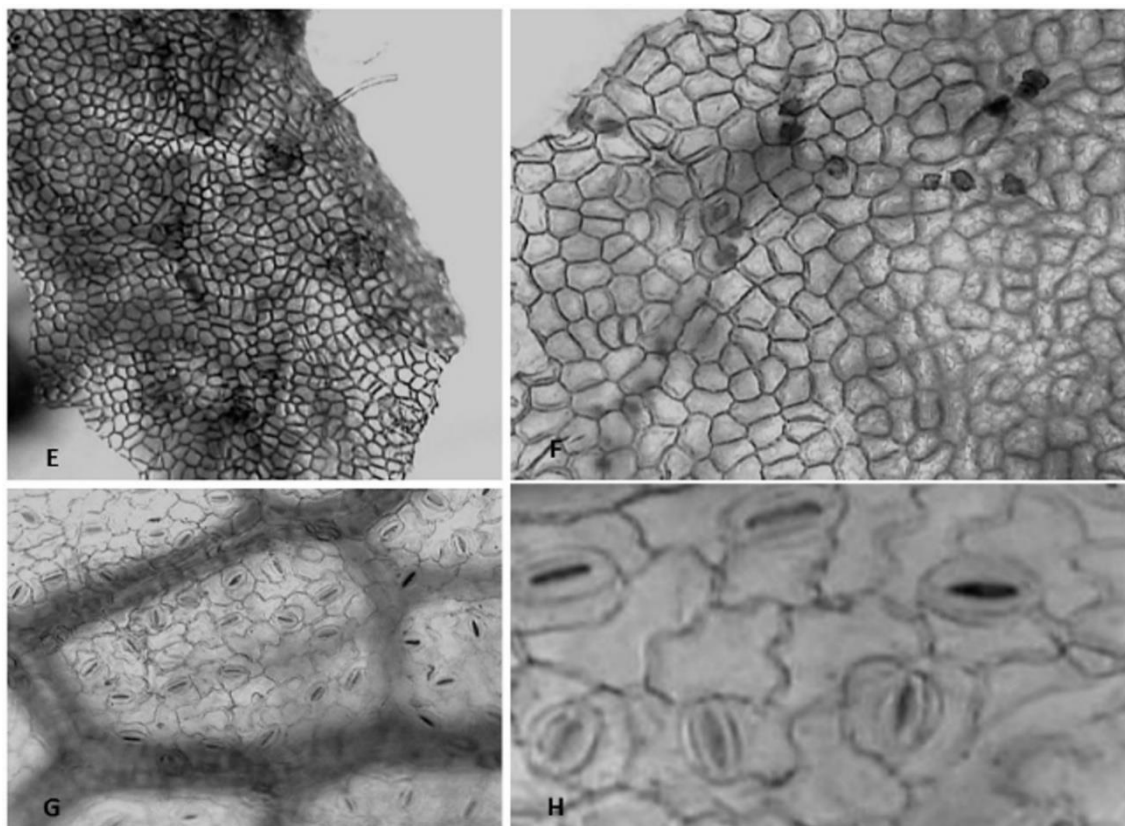
In the evaluation of authenticity in the study of the anatomical sample 5, released as a drug in a sachet, showed the presence of crystals of calcium oxalate, druse type; the epidermis with some pockets of secretory cells, straight or slightly sinuous anticlines walls, paracitic and anomocytic stomata and, in addition, long unicellular tectorial trichomes (Figures 1 and 2). All of these structures have been described for the species *Passiflora edulis* in an official monograph in the Brazilian Pharmacopoeia (BRAZIL, 2019) verifying the sample authenticity.

**Figure 1.** *Passiflora incarnata* L. (sample 5: drug in sachet). A and B: crystals of calcium oxalate, druse type; C: pockets of secretory cells; D: unicellular tectorial trichomes





**Figure 2.** *Passiflora incarnata* L. (sample 5: drug in sachet). E: straight or slightly sinuous anticlines walls. F: cell wall thickening, and presence of druses. G and H: epidermis with paracytic and anomocytic stomata.



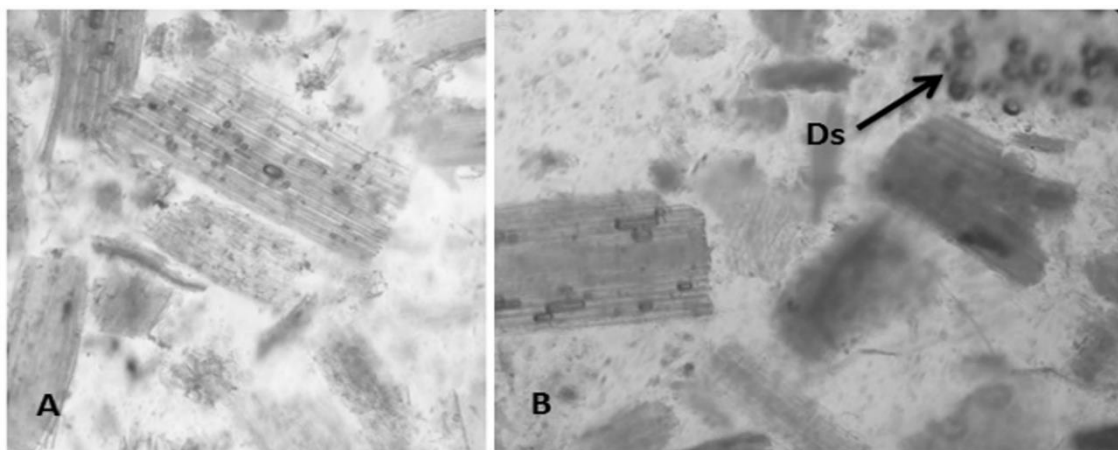
In sample 4, it is also marketed as a drug, but in the form of a capsule, the anatomical studies were prejudiced, given the small size of the particles, which is illustrated only in the presence of the fragments of the epidermis, with crystals of calcium oxalate (druses) (Figure 3), making it difficult, therefore, the evaluation of the authenticity of the drug in the plant based on the conventional analysis by electron microscopy of vegetable. In this way, we evidence the necessity for more effective and sensitive techniques to assess drug authenticity, as an example of the technique of *Barcode* DNA.

Samples of the dried extract in capsules (1, 2, and 3) were also subjected to microscopic examination in order to verify the presence of plant tissue and/or undeclared excipients. In this analysis, it was shown that sample 2 presented excipients in its composition, which are represented by the white color particles, which differs from the content of the other samples, who showed only the particles in shades of yellow.

According to Santana et al. (2007), the use of dried herbal extracts, as raw material for herbal medicines provides a number of advantages compared to the use of the plant in

the form of a powder (vegetal drug), with the standardization of assets, greater the conservation and the elimination of undesirable substances.

**Figure 3.** *Passiflora incarnata* L. (sample 4: drug in capsule). A: fragments of epidermis and mesophyll. B: crystals of calcium oxalate (druses)



However, this form of presentation does not reduce the risk of adulteration by adding non-pharmacological action and is not stated on the packaging in its composition. The presence of excipients can provide the quality problems, such as a lower amount of the active ingredient than stated on the label, creating consequently sub-therapeutic doses; or the heterogeneous distribution of the drug in each unit dose from the same bottle, making the release of the active ingredient irregular during treatment (MARKMAN et al., 2010).

In addition to the morphoanatomical aspects, microbiological control is indispensable in order to ensure the quality of the botanical material. Uniform inoculation of aliquots from the commercial samples under study in the BHI media in broth and MacConkey agar plates resulted in the clouding of the broth and the growth of untold numbers of bacterial colonies on the plates of the drug in sachet (5), proving the bacterial contamination in any of the steps of the tests. In all the other seeded spots with a sample in the capsules (1, 2, 3, and 4) there was no bacterial growth.

The results obtained in the microbiological control of the samples allowed us to observe that one of the samples (5) was outside the limits permitted by the World Health Organization, ( $10^5$  CFU/g) and in Brazilian Pharmacopoeia ( $10^3$  CFU/g) for domestic use of the vegetal drug (WHO, 1998; BRAZIL, 2019). It is worth emphasizing that, as noted

earlier in this study, this sample also showed the amount of foreign matter is much higher than the permissible limits.

A local study (GONÇALVES, 2016) proves the poor microbiological quality of the vegetal drug for medicinal use sold in São Luís; highlighting, as well as in the present study, that the purchase of plants and plant-derived products carry risks, not only if purchased in the informal sector, in markets and free markets, but also in pharmaceutical establishments under the technical responsibility of the pharmacist.

In the comparison between the drugs samples of the study (4 and 5) with the monographs of the drugs, *Passiflora incarnata* and *Passiflora alata* (Brazilian Pharmacopoeia, 2019) for foam index tests ( $\leq 100$ ), humidity (10%) and total ash (15%), the sample 4 had a foam index  $<100$ , the water content of  $8.81 \pm 0.02\%$  and total ash content of  $14.81 \pm 0.29\%$ , while sample 5 presented an index of foam  $<100$ , with a water content of  $8.36 \pm 0.06\%$  and ash content of the total  $4.57 \pm 0.004\%$ . The data attest that both of the samples had values within the limits of the three parameters to guarantee the purity of the drug in the plant.

But it is worth emphasizing that the determination of the values of the indices of the foam, in samples 4 and 5 under the limit determined by the Brazilian Pharmacopoeia (BRAZIL, 2019) indicating a subjective quality parameter regarding chemical integrity regarding the composition of saponins (glycosides, steroids or terpenes polycyclic, with the ability to act on cell membranes, causing changes in the permeability, or lead to destruction) (SIMÕES et al., 2017). The values of the total ash samples in the study, within the framework of the pharmacopoeia, also suggest the quality of the material and the absence of the non-volatile inorganic contaminant (SIMÕES et al., 2017; BRAZIL, 2019).

The findings of water contents on the samples in the study that are inside the pharmacopoeial limits indicate a quality parameter considering that high water content in plant material favors the action of enzymes and the development of microorganisms, which can lead to the degradation of active substances and interfering, consequently, in the pharmacological value (SIMÕES et al., 2017).

The determination of the quality and integrity of the plant material, aiming at the evaluation of the loss of one or more of its chemical and biological properties, is carried out through a qualitative and quantitative analysis of markers active and/or analytical,

represented by classes of substances that are used as a reference in the area of quality control (BRAZIL, 2014).

Studies have shown that the major chemical constituents of the genus *Passiflora* are alkaloids, phenols, and glycosylated flavonoids and the flavonoids are the most representative; which are attributed to biological activities already evidenced in the species (DE-PARIS et al., 2002). Previous studies have addressed the specific differences in the identification and quantification of flavonoids in the species of *Passiflora alata* and *Passiflora edulis*, in addition to a greater number of vitexin and apigenin in the *Passiflora alata* and isovitexin on *Passiflora edulis* (MÜLLER, 2005). Thus, the study of the control of the quality of the species of *Passiflora* should be grounded in the flavonoid investigation, in accordance with the requirements of the Brazilian Pharmacopoeia (BRAZIL, 2019).

The most appropriate methodology for the identification and quantification of flavonoids is the total sample of vegetables is analyzed by high-pressure liquid chromatography of high efficiency, however, it is necessary to look for a simpler and more affordable alternative for use in the control of quality, given that the pharmaceutical sector need of a quick answer. One of the main techniques that are used for this replacement is to be determined by the method of spectrophotometric in the UV, with the use of aluminum chloride (FIGUEIRÊDO et al., 2015).

The content of flavonoids in the total of samples 1 and 2 (5.53 and 3.35%, respectively) was above the cited in the literature for the *Passiflora incarnata*, in the form of a dried extract (minimum of 1.5% of total flavonoids expressed as vitexin) (French Pharmacopoeia, 1992). Sample 3 (0.9%) also showed a higher content of flavonoids in total to a minimum of 0.55% of the total flavonoids expressed as apigenin) for the dry extract of *Passiflora alata* (PETRY et al., 1998).

However, samples 4 and 5 (0.247 and 0.239%) were found with the values of the flavonoids lower than that which is required in another study (BRAZIL, 2019) of the genus *Passiflora* (less than 1% of total flavonoids expressed as apigenin).

The total flavonoid contents were different in all samples, including those with the same presentation form. These differences may be explained by the origin and quality of the plant material, the different modes of drying used in drugs, plants, and/or by different methods of extraction for each of the samples of the dried extract subjected; with the use of the factors that may influence the extraction, such as heat. The literature

emphasizes that the increase of the temperature in the extraction process of thermoresistant drugs can influence it in a positive way, leading to an increase in the solubility of a given active ingredient, an increase in the speed of diffusion, and a decrease in the viscosity of the solvent, so the hot extraction processes it is faster than the one carried out in the ambient temperature (SIMÕES et al., 2017).

## CONCLUSION

The results of this study demonstrate the poor quality (color, medium-weight, foreign materials, microbial contamination, and/or content of flavonoids) of the samples marketed for therapeutic purposes, such as passion fruit, evidencing the need for surveillance, monitoring, and control of the quality of the medicinal plant material available for sale, which will require effective action in the area of Pharmacovigilance in Herbal medicine from the real perspective of minimizing the risks of the therapeutic use of unsuitable material for consumption.

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*Recebido em: 08/11/2022*

*Aprovado em: 10/12/2022*

*Publicado em: 16/12/2022*