ARTICLE
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Quality control of the plant drug *Calendula officinalis* L. available in the city of Ponta Grossa (PR)

Controle de qualidade da droga vegetal *Calendula officinalis* L. disponível na cidade de Ponta Grossa (PR)

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ABSTRACT

Introduction: *Calendula officinalis* L. is a herbaceous plant belonging to the Asteraceae family that contains flowers as parts used to obtain analgesic, anti-inflammatory, antiseptic, healing, and dermoprotective effects. **Objective:** The objective of the present work was to analyze and characterize samples of *C. officinalis*, sold in Ponta Grossa (PR), and verify their compliance with current legislation, presenting the quality control provided for by the Brazilian Pharmacopoeia (2019). **Method:** After selecting the selections, tests were carried out on the quality control of the herbal drug by checking the packaging and labeling, macroscopic and microscopic identification, purity tests, analysis of loss due to desiccation and total ash, thermal analysis, profile of the aqueous extract in thin layer chromatography, and source of flavonoids from secondary metabolites. **Results:** All samples were identified as *C. officinalis* and were approved in the chromatographic profile and flavonoid content; however, sample B did not meet the pharmacopoeia purity requirements. **Conclusion:** Medicinal plants with quality deviations may suffer a significant reduction in their therapeutic effect, in addition to generating possible side and toxic effects.

KEYWORDS: Thermal analysis; Flavonoids; Medicinal Plants; Purity

RESUMO

Introdução: A *Calendula officinalis* L. é uma planta herbácea pertencente à família Asteraceae que possui as flores como partes utilizadas visando a obtenção de efeitos analgésicos, anti-inflamatórios, antissépticos, cicatrizantes e dermoprotetores. **Objetivo:** Analisar e caracterizar amostras de *C. officinalis*, comercializadas em Ponta Grossa (PR) e verificar sua adequação conforme a legislação vigente, apresentando o controle de qualidade previsto pela Farmacopeia Brasileira. **Método:** Após a seleção das amostras foram realizados testes acerca do controle de qualidade da droga vegetal por meio da verificação da embalagem e rotulagem, identificação macroscópica e microscópica, ensaios de pureza, análise de perda por dessecação e cinzas totais, análise térmica, perfil do extrato aquoso em cromatografia em camada delgada e determinação de flavonoides a partir dos metabolitos secundários. **Resultados:** Todas as amostras analisadas foram identificadas como *C. officinalis* e aprovadas no perfil cromatográfico e no teor de flavonoides, contudo, a amostra B não atendeu aos requisitos farmacopeicos de pureza. **Conclusões:** Plantas medicinais com desvios de qualidade podem sofrer redução significativa de seu efeito terapêutico, além de gerar possíveis efeitos colaterais e tóxicos.

PALAVRAS-CHAVE: Análise Térmica; Flavonoides; Plantas Medicinais; Pureza

INTRODUCTION

Society has always used products of plant origin to meet basic survival needs and to make homemade preparations to treat and/or prevent illnesses. It is worth mentioning that much of this knowledge is still valid today. In this context, it is known that the consumption of medicinal plants and herbal drugs has increased among the population, a fact mainly attributed to the high cost of synthetic medicines and their continuous use. Therefore, the lack of access to synthetic medicines, the appreciation of products of natural origin, the proof of the therapeutic action of various medicinal plants, as well as the fact that there is no need for a doctor's prescription for the use of these plants and other herbal drugs, have all contributed to a gradual and accentuated rate of use of natural therapies.[1]

According to the World Health Organization (WHO)[2], medicinal plants are "any plant that contains, in one or more organs, substances that can be used for therapeutic purposes or as sources of drugs and their precursors". The search for phytotherapy is the result of the search for pharmacotherapeutic procedures that combine efficacy with a low incidence of side effects. Given this fact, many medicinal plants still need more detailed scientific studies, including, above all, clinical evaluation, whose function is to ascertain safety and performance, with quality control being an indispensable practice at this stage.[3]

The safety and efficacy of medicinal plants depend on numerous factors, such as the quality of the product being marketed. Therefore, quality control goes beyond the set of laboratory operations, as explained in Collegiate Board Resolution (RDC) No. 17 of April 16, 2010[4], which sets out parameters related to sampling, organization, documentation, and other release procedures. Thus, the existence of a standard for the commercialization of medicinal plants guarantees the quality and, therefore, the efficacy of these products, guaranteeing the appropriate treatment of physiopathological processes.[5]

The quality of medicinal plants is mainly determined by the content of active compounds, which are responsible for the therapeutic effects, and the absence of contaminants. As such, marketing fraud and aspects related to poor quality are a cause for concern in the scientific community, as they directly interfere with the efficacy and safety of the product.[6]

It should be noted that herbal and plant drugs should not be confused, because although both are obtained from medicinal plants, they are manufactured differently. While herbal drugs are more elaborately produced and presented in the final form of use, be it capsules, tablets, or syrups, plant drugs are made up of the dried plant, whole or torn up, for use in the preparation of medicinal teas.[7]

Calendula officinalis L. is an herbaceous plant belonging to the Asteraceae family, popularly known as calendula, marigold, and golden daisy[8]. Its most commonly used part is the flower, which has analgesic, anti-inflammatory, antiseptic, and dermoproteric effects[1]. Consequently, externally, the medicinal plant acts to prevent infections in wounds and abrasions and, internally, it acts prophylactically against glandular and vascular inflammation. It also has toning and vasodilating effects. [9]

The therapeutic properties of this medicinal plant, which is native to Central and Southern Europe, Western Asia, and the United States, are due to the numerous classes of phytoconstituents, such as terpenoids, saponins, flavonoids, alkaloids, coumarins, quinones, carotenoids, and volatile oils, as well as significant amounts of carbohydrates, amino acids and lipids.[10]

The botanical characteristics of *C. officinalis*, an annual herb about 50 cm high, include thick, green, whole, hairy leaves. The flowers, on the other hand, are yellow and are gathered in chapter-type, auxiliary, and terminal inflorescences. The fruit is dried achene. It's worth noting that planting is done through seeds and there is a need for well-drained soil with a high organic matter content, especially when forming seedlings and during the flower bud stage; the crops are extremely sensitive to high temperatures. Finally, floral subunits are collected three months after planting and dried in the shade.[11]

METHOD

Three 90 g samples of *C. officinalis* flowers sold as a plant drug in the region of Ponta Grossa, in the state of Paraná (PR), identified as samples A, B, and C, were selected. It should be noted that the samples were acquired from different places of sale, including pharmacies, healthy food stores, and supermarkets.

All the samples analyzed came from companies registered with the Brazilian Ministry of Health. Tests were then carried out for macroscopic identification, microscopic identification, foreign material, moisture determination, total ash determination, and thermal analysis. All the tests, apart from the thermal analysis carried out at the Multiuser Sebisa Laboratory at the State University of Ponta Grossa (UEPG), were carried out on the premises of the Chemistry Laboratory at *Faculdade Cesumar de Ponta Grossa* (UniCesumar). The aqueous extract was obtained from the plant and then the total flavonoids were determined and quantified using thin-layer chromatography (TLC). It should also be noted that the information on the packaging and labeling was analyzed to check that it complied with the standards recommended by RDC No. 26/MS/SNVS[12], of May 13, 2014, and article 57 of the Consolidated Standards for Registration and Notification of Herbal drugs.[13]

The macroscopic analysis was carried out through a visual and sensory examination using a stereoscopic microscope, as described by the Brazilian Pharmacopoeia[14]. This method is simple for checking quality-related parameters, especially regarding aspects of identity and purity[15]. The mass of 5 g of each sample was determined and then stored in 70% alcohol for cell hydration for 7 days. Slides were mounted in 50%

glycerine and stained with SUDAN III, 0.0125% basic fuchsin and 1% Astra blue.[16]

During the purity test, carried out in triplicate, 10 g of each sample were analyzed by separating foreign materials from the plant drug, such as insects and parts of other plants. These materials were then weighed, and the percentage of impurities was determined and expressed as the mean, standard deviation, and coefficient of variation.[14]

For moisture analysis, a gravimetric method based on loss on drying in an oven at 105 °C for 2 hours was used. 1 g of each sample was weighed in a Petri dish. The samples, after being heated and cooled to room temperature in a desiccator, were weighed again until a constant weight was obtained. The tests were carried out in triplicate. At the end of the procedure, the percentage of water in relation to the plant drug was determined, with results expressed as mean, standard deviation and coefficient of variation. [14]

Total ash was analyzed by incinerating 1 g of the plant drug in a muffle furnace at 600°C for 6 hours. After incineration, the samples were cooled to room temperature in a desiccator and weighed again until a constant weight was obtained. The tests were carried out in triplicate. At the end of the procedure, the percentage of ash in relation to the plant drug was determined, with results expressed as mean, standard deviation and coefficient of variation.[14]

To carry out the phytochemical tests, aqueous extracts were prepared from 30 g of each sample, which were macerated in water at a temperature of between 30 and 40°C. The flavonoids in the extract were detected using TLC. The stationary phase consisted of a 10 x 10 cm chromatoplate with a 25 mm layer of silica gel 60 (Macherey-Nagel). A mixture of ethyl acetate, anhydrous formic acid, and distilled water (80:10:10) was used as the mobile phase. Rutin was used as a chromatographic standard. The chromatoplate was then air-dried and 365 nm ultraviolet light was applied. After this, it was developed with anisaldehyde sulphur. Finally, the chromatoplate was placed in an oven at 105°C and its retention coefficient (R_f) was calculated by dividing the distance traveled by the substance by the distance traveled by the mobile phase.[14]

The total flavonoid content of *C. officinalis* was quantified according to the methodology described by Santos[17]. A calibration curve was prepared using rutin solutions at concentrations of 5 to 50 µg mL^{-1}. 400 µL of the rutin solutions, 200 µL of 2.5% aluminum chloride, 200 µL of 10% sodium acetate, and 4 mL of ethanol were added to a test tube. The blank test was prepared with 4.4 mL of ethanol, 200 µL of aluminum chloride, and 200 µL of sodium acetate. The tubes were shaken and then left to stand for 40 min. Readings were taken on a BEL photonics® spectrophotometer at 425 nm. The test was carried out in triplicate. Finally, the total flavonoid content was determined in milligram equivalents of rutin per gram of crude extract, using the following equation based on the calibration curve: y = 0.1854x - 7E-05, where R^2 = 0.9924.

The last analysis carried out aimed to evaluate the thermal degradation of *C. officinalis* flowers using thermogravimetry. Thermogravimetry curves were obtained from 5 mg samples of the plant drug, which were heated at a constant rate of 10°C min^{-1}, and obtained in the temperature range between 20 and 650°C, under nitrogen flow (50 mL min^{-1}), in an open alumina calorimetric cell. The STA 6000 instrument (Perkin-Elmer, Whaltam, MA, United States) was calibrated using Indium (In; PF: 156.6°C; ΔH_{fusion}: 28.54 J g^{-1}) as a standard. The thermoanalytical study of *C. officinalis* flowers was carried out using the Origin 9.0 program for statistical adjustments.

RESULTS AND DISCUSSION

About packaging and labeling, the Ministry of Health's RDC No. 26[16] stipulates that the trade name, popular nomenclature, official botanical nomenclature, part used, dosage, net weight, form of use, expiry date, batch, date of manufacture, company name, name of the pharmacist responsible, Regional Pharmacy Council (CRF), National Register of Legal Entities (CNPJ), mandatory phrases, full address, customer service number (SAC), and bar code must be present on the labels of herbal products. In this sense, sample A was approved, unlike samples B and C, which did not present the official botanical nomenclature, the part to be used, the pharmacist responsible, and the registration with the professional council. It was also found that sample C did not show the batch. Therefore, it can be seen that the consumer does not receive complete information about the product purchased, as recommended by current legislation.

The botanical description of *C. officinalis* indicates that the plant has a weak, pleasantly aromatic smell with a bitter taste. In addition, its flowers should be ligulate, yellowish, yellow-orange to brownish-orange in color, with an extremely hairy short tube and a tridentate ligule at the apex, with four or five parallel veins; occasionally the flowers may be accompanied by a filiform stipe and a bifid stigma. The fruits, when present, have curved, navicular achenes, with the back covered in short spines and a greenish-brown color[14]. It was therefore possible to see that all the samples matched the description of the flowers and the sensory characteristics of *C. officinalis* (Figure 1).

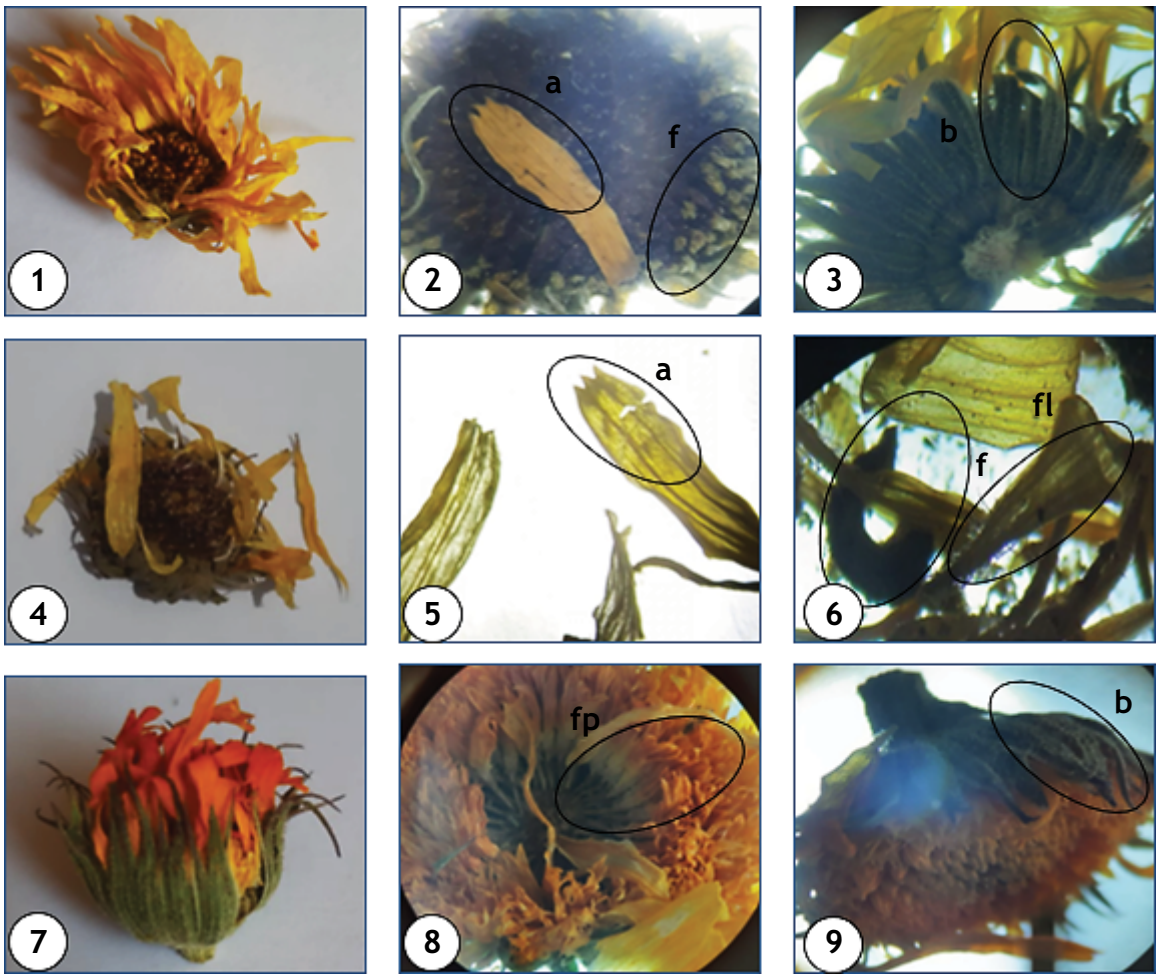
Authentic samples of *C. officinalis* should contain ligulate pistillate flowers, tubular disc flowers, anthers of the tubular flower with pollen grains, multicellular biseriate trichome of the corolla tube of the ligulate flower, fragment of the ligule, detail of the end of the fragment of the ligule with oil drops in the parenchyma, fragment of the epidermis of the ligule with striated cuticle, fragment of the parenchyma of the ligule containing oil drops, aspect of the fruit and tricolpate pollen grains[14]. All the samples were approved (Figures 2, 3, and 4).

Regarding the purity test, Brazilian legislation allows up to 3% impurities in the methodology used[14]. As a result, sample B failed, with an average percentage of impurities of 4.8%, in

which the standard deviation was 0.2 and the coefficient of variation was 4.2%. Parts of other plant species were found in this sample, indicating cross-contamination or inadequate separation and cleaning processes[18], insects, and dust, possibly from the disintegration of the plant drug. In addition, the presence of fruit in sample B indicates that the floral chapters were collected at the wrong time, as they should be collected before the fruit is formed[17]. Therefore, the results obtained in this test highlight the importance of each stage of production, as the inadequacy of these processes has a direct impact on the quality and quantity of the active compounds present in plant drugs, nullifying their therapeutic efficacy and also posing risks to the health of the consumer. [6]

In the desiccation loss test, sample A had an average of 9.2%, with a standard deviation of 0.3 and a coefficient of variation of 3.2%. Sample B had values of 10.1%, 0.4, and 3.9%, while sample C had values of 9.8%, 0.2, and 2.0%. Therefore, as the Brazilian Pharmacopoeia[14] recommends a maximum limit of 12.0% moisture in this test, all the samples were approved. It should be emphasized that excess water in plant drug samples favors enzymatic activity and the proliferation of microorganisms that break down the active compounds of the medicinal plant and is therefore detrimental to the quality of the product.[19]

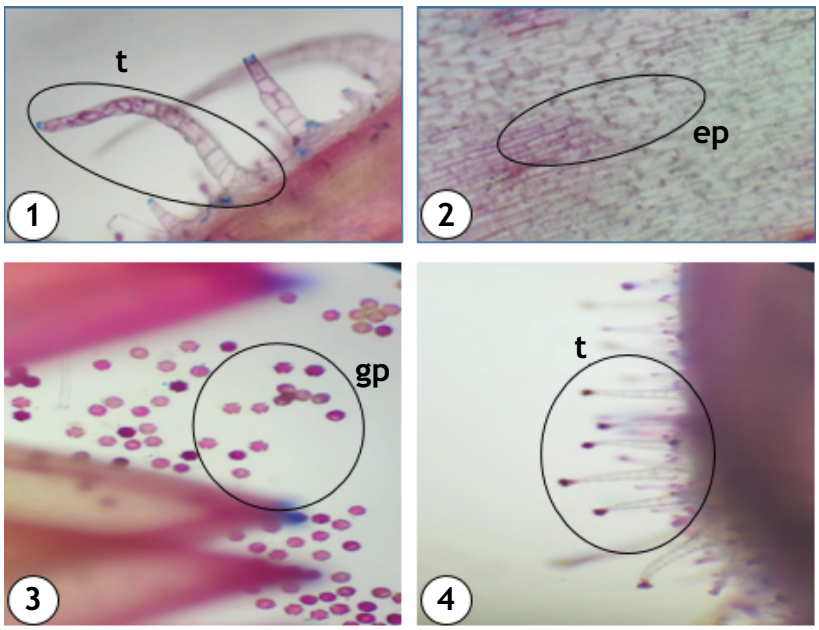
It is known that the ash content refers to inorganic residues such as stones, cement, and sand[20], or fixed mineral residues such as sodium, potassium, magnesium, calcium, iron, phosphorus, copper, chloride, aluminum, zinc, manganese, and others, left over from the burning of organic matter[21]. Therefore, in this context, sample A had an average of 7.9% for the total ash analysis, with a standard deviation of 0.7 and a coefficient of variation of 8.8%. Sample B had values of 9%, 0.6, and 6.7% respectively, while sample C had values of 7.0%, 0.2, and 2.8%. As the maximum limit is 10.0% according to current legislation[14], all the samples were approved.



Sample A: 1. coloration; 2. ligulate flower tridentate at the apex (a) and fruit (f); 3. bract (b); Sample B: 4. coloration; 5. ligulate flower tridentate at the apex (a); 6. fruit (f) and ligulate pistillate flower (fl); Sample C: 7. coloration; 8. small ligulate flowers (fp); 9. bract (b).

Source: Prepared by the authors, 2021.

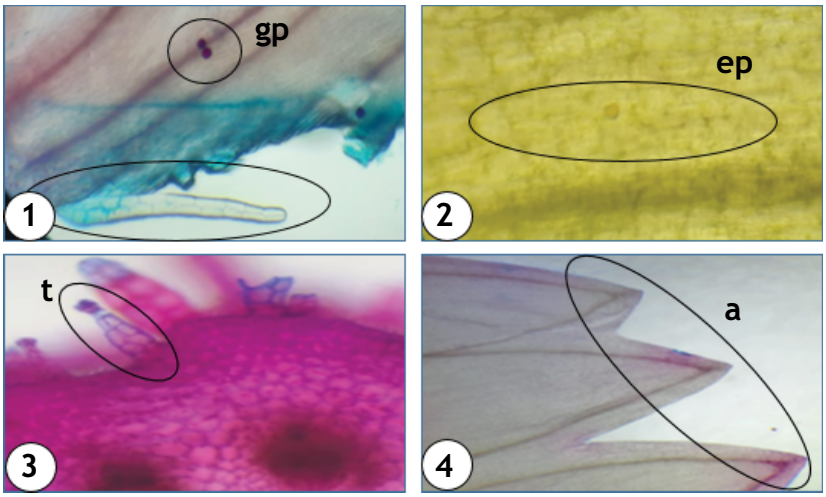
Figure 1. Macroscopic analysis of *Calendula officinalis* L.



1. Bisected multicellular trichome of the corolla tube of the ligulate flower (t); 2. Fragment of epidermis of the ligule with striated cuticle (ep); 3. Tricolpate pollen grains (gp); 4. Bisected multicellular trichome of the corolla tube of the ligulate flower (t); Staining with basic fuchsin 0.0125% and Astra blue 1%.

Source: Prepared by the authors, 2021.

Figure 2. Microscopic analysis of sample A of *Calendula officinalis* L.



1. Tricolpate pollen grains (gp) and bisected multicellular trichome of the corolla tube of the ligulate flower (t); 2. Fragment of the epidermis of the ligule with striated cuticle (ep); 3. Bisected multicellular trichome of the corolla tube of the ligulate flower (t); 4. Ligulate flower 3-toothed at the apex (a); 1, 3, and 4 - Staining with 0.0125% basic fuchsin and 1% Astra blue; 2 - Staining with SUDAM III.

Source: Prepared by the authors, 2021.

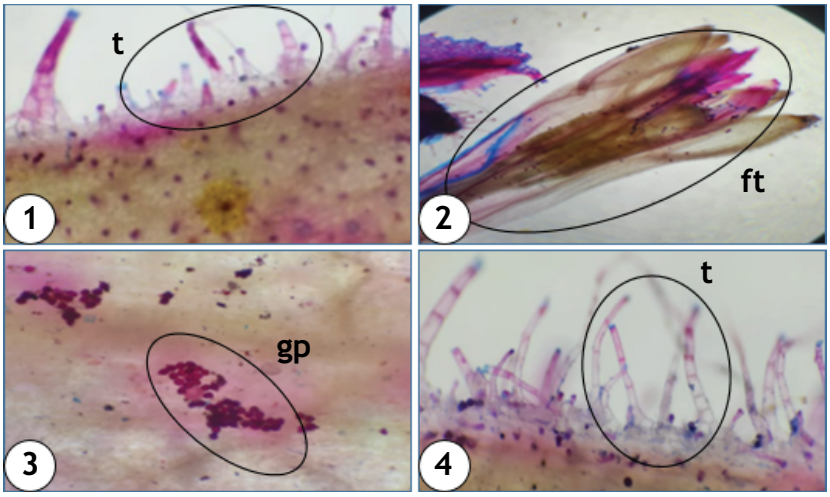
Figure 3. Microscopic analysis of sample B of *Calendula officinalis* L.

Regarding the phytochemical tests, when the chromatogram was made, samples A, B, and C had the same R_f = 0.46, while the R_f for rutin was 0.44. CCD was therefore efficient in establishing a chromatographic profile for the *C. officinalis* extract. It should be noted that the results indicate the presence of rutin, a flavonoid characteristic of this plant drug. Furthermore, with the application of ultraviolet light at 365 nm, with R_f = 0.73, the presence of aglycones, flavonols, and biflavonoids was observed[20]. Flavonoids are among the most important groups in the kingdom and are phenolic compounds, i.e. they have antioxidant capacity attributed to the reducing power of the aromatic hydroxyl group, which reduces reactive free radicals.

The antioxidant capacity of these compounds is influenced by the number and position of the hydroxyl groups, as well as the glycosylation positions, thus facilitating or hindering the donation of protons to reactive species.[22]

When the flavonoids were quantified, sample A was found to contain 0.1231 mg/g of rutin, sample B 0.1771 mg/g, and sample C 0.1082 mg/g. The Brazilian Pharmacopoeia[14] recommends that plant drugs made from *C. officinalis* should contain at least 0.4 mg/g of rutin. Therefore, all the samples failed. This could be due to inadequate conditions during the production process of the plant drug, leading to the degradation of active ingredients[17]. In addition, natural factors such as solar radiation, ultraviolet rays, dry or rainy periods, and the season can influence the metabolism and production of these compounds. Artificial factors, such as pollutants, also affect the production and stability of active compounds.[23]

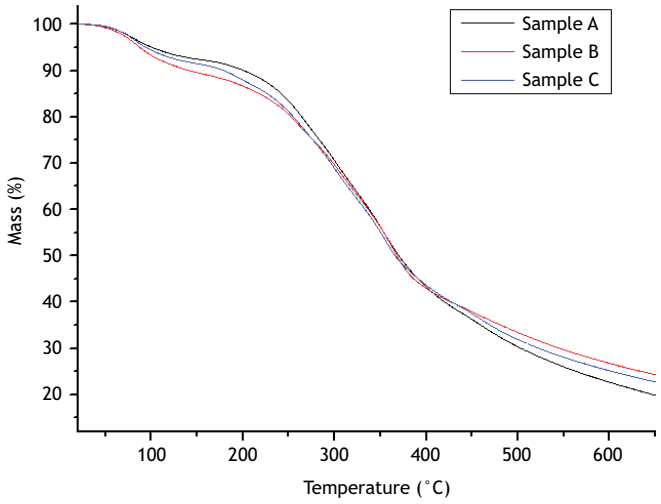
When evaluating the thermogravimetric profile of the plant drug samples, three stages of thermal composition were found, i.e. it can be said that the thermodynamic behavior of the *C. officinalis* flower samples is similar, indicating that they belong to the same species. It should be noted that the small differences in the temperatures corresponding to the maximum degradation peaks are related to the degradation of hemicelluloses and cellulose[24] (Graph).



1. Bisected multicellular trichome of the corolla tube of the ligulate flower (t); 2. Tubular flower of the disk (ft); 3. Tricolpate pollen grains (gp); 4. Bisected multicellular trichome of the corolla tube of the ligulate flower (t); Staining with basic fuchsin 0.0125% and Astra blue 1%.

Source: Prepared by the authors, 2021.

Figure 4. Microscopic analysis of sample C of *Calendula officinalis* L.



Source: Prepared by the authors, 2021.

Graph. Thermogravimetric curve for the heating ratio in a nitrogen atmosphere.

During the first stage of thermal degradation, there is a process of dehydration, characterized by the release of water from the cell wall[24]. This phase, in sample A (4%), occurred in the temperature range of 20 °C to 83 °C, while for sample B (5) it occurred between 20 °C and 85 °C, and in sample C (4.5%), between 20 °C and 83 °C. In the second stage of thermal degradation, there is a marked loss of mass, mainly due to the oxidation and degradation of organic matter, such as some secondary metabolites[25]. For sample A (46.0%) it occurred in the temperature range of 83 to 367 °C, for sample B (48.0%) in the range of 85 to 374 °C, and finally, in sample C (45.0%), it was between 83 °C and 362 °C, representing the degradation of metabolic compounds. The third and final stage has a slower decomposition of polymer chains, carbon residues and more fibrous parts, such as cellulose and lignin[26]. For sample A (20.0%) it occurred in the temperature range 367 °C to 650 °C, for sample B (24.0%) it was in the range 374 °C to 650 °C, while for sample C (23.0%) it varied between 362°C and 650°C. If the method had been carried out in an oxygen atmosphere, all the carbon would have been burnt off, leaving ash. However, as the method was carried out in a nitrogen atmosphere, there was no ash left over, but rather carbon residue, which was 30.0%, 23.0% and 27.5% for samples A, B, and C respectively.

CONCLUSIONS

The tests carried out showed that certain samples failed the packaging and labeling analysis, as well as the percentage of impurities. It was therefore possible to conclude that all the *C. officinalis* samples, in at least one of the tests, did not comply with the standards recommended by the Brazilian Pharmacopoeia. Therefore, it can be seen that the quality of some of the plant drugs sold is unsatisfactory, and there is a need for greater intensification in the health surveillance of medicinal plant-based products sold in Brazil.

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Authors' Contribution

Nunes GAC - Conception, planning (study design), acquisition, analysis, data interpretation, and writing of the paper. Lacerda IJM - Writing the paper. Swiech JND - Conception, planning (study design), data interpretation. All the authors approved the final version of the paper.

Conflict of Interest

The authors inform that there is no potential conflict of interest with peers and institutions, political or financial, in this study.