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Original Article

STANDARDIZATION AND STABILITY EVALUATION OF DRY EXTRACTS OF *MYRACRODRUON URUNDEUVA* ALLEMÃO OBTAINED BY SPRAY DRIER

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ABSTRACT

Objective: This study aimed to obtain standardised dry extracts of *Miracrodruon urundeuva* Allemão using spray-dryer and evaluate the stability of the extracts.

Methods: It evaluated the drying parameters: Proportion of colloidal silicon dioxide (CSD) (10, 15 and 20%), inlet temperature (160, 170 and 180 °C) and feed rate (4, 6 and 8 ml/min). The study of the accelerated stability of dry extract occurred in temperature of 40 °C (±2 °C) and relative humidity of 75% (±5%) for 6 mo. The anti-inflammatory activity of the dry extract was evaluated in Swiss mice by the paw edema method.

Results: Variations in drying conditions did not represent significant variations in yields of the process. The drying temperature and feed rate significantly influenced the concentration of quercetin ($p \leq 0.05$). The increase in inlet temperature and feed flow promoted the increase of quercetin concentration in the extracts. The stability study showed that the concentration of quercetin in dry extract was stable over a period of 6 mo. The dry extract showed anti-inflammatory activity in mice orally.

Conclusion: A condition of 10% of colloidal silicon dioxide with an 180 °C inlet temperature and a feed rate of 8 ml/min was considered the most adequate for obtaining the extracts and the drying process resulted in stable dry extracts and the quercetin was a suitable biomarker for monitoring the process.

Keywords: *Myracrodruon urundeuva* Allemão, Dry extracts, *Spray dryer*, Stability

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INTRODUCTION

The *Miracrodruon urundeuva* Allemão is an arboreal species of the Anacardiaceae family, which is native to Brazil but also found in Mexico, Argentina, Bolivia and Paraguay, that is used in folk medicine for its medicinal properties [1]. Studies using extracts from different parts of this plant have shown anti-ulcer activity [2-4], anti-inflammatory and wound healing properties [4, 5], antibacterial and antifungal properties [6], neuroprotective qualities [7] and cytotoxicity in cancer cells [8].

The study of an ethanolic extract of leaves of *M. urundeuva* showed a higher incidence of secondary metabolites in the species than those derived from phenolic acids [9]. Phytochemical studies of the stem and leaf showed the presence of tannins, flavonoids, mono and sesquiterpenes, triterpenes and steroids, condensed proanthocyanidins and leucoanthocyanidins and sugars [10, 11].

Quercetin is a flavonoid identified in *M. urundeuva* known to express pharmacological activity as an antioxidant, anti-inflammatory and antimicrobial, among others [12-16]. Thermoanalytical studies indicate that this compound is stable up to 315 °C when it starts the process of decomposition [17].

The development of standardised plant derivatives with defined chemical, physical, and technological characteristics is fundamental in the herbal industry and results in obtaining pharmaceutical forms with assured quality to ensure reproducibility in the preparation of a medicinal product and its therapeutic efficacy [18].

The use of dry extracts in the production of herbal medicines has been employed due to their greater chemical stability; physiochemical and microbiological characteristics; higher concentrations of active compounds; ease of patterning and handling; and greater processing capacity in different pharmaceutical formulations than liquid extracts [19, 20].

Among the techniques successfully employed in the preparation of dry plant extracts is the nebulization by spray drying, which produces powders with defined characteristics, such as shape and particle size, and the rapid evaporation of the solvent reduces the process time and risk of changes of thermolabile products [21-24].

This study aimed to obtain standardised dry extracts of *Miracrodruon urundeuva* Allemão using spray drying and to evaluate the stability and anti-inflammatory activity of the dry extracts obtained.

MATERIALS AND METHODS

Plant material and chemicals

This study used leaves of *Myracrodruon urundeuva* Allemão (Anacardeaceae) collected from farms in Cacimbas and Caraúbas in the state of Paraiba, Brazil. Entire plants were collected during the flowering stage. A representative sample of this species is deposited in the Lauro Pires Xavier Herbarium of the Federal University of Paraíba (Registration no. NC240) and botanical identification was carried out by Professor Alecksandra Vieira Lacerda of the Federal University of Campina Grande. The plant material was dried at 50+2 °C for 96 h in a circulating air oven, reduced to a powder in a mechanical mill, and stored in sealed plastic bag. The hydroethanolic extract of the plant was obtained by the maceration at 25 °C of 2 kg of powdered leaves in 10l of ethanol/water solution 50% (v/v) for 120 h.

HPLC grade solvents were purchased from Tedia Co. (Phoenix, AZ-USA). The standard employed in the analyses was quercetin dehydrate CAS–117-39-5 (97% pure) that had been acquired by Merck, Brazil. The colloidal silicon dioxide (Henrifarma, Brazil) was used as a drying agent. Carrageenan (Sigma-Aldrich, Brazil) and diclofenac sodium (Novartis, Brazil) were used in the study of the anti-inflammatory activity.

Spray-drying

The spray-drying process was performed in a laboratory-scale model SD-05 (Lab-Plant, Hudders field, UK). The atomiser double pneumatic fluid nozzle with 1.2 mm opening hole operated with an airflow rate of 62 m^3/h and a 2.0 bar of pressure. A 2^{3+1}factorial experimental design was used to assess the effect of spray-drying operating variables on yield and quercetin concentration on the drier extract. Three factors at two levels were considered: (A) drying air inlet temperature (160, 170 and 180 °C), (B) the flow rate of the drying composition fed to the spray drying (4, 6 and 8 ml/min) and (C) the proportion of colloidal silicon dioxide (CSD) (10, 15 and 20%). Table 1 summarises the levels of operating variables.

The silicon dioxide was selected for the study because it is an adjuvant with a high surface area and thermal stability, it is a safe excipient when used in pharmaceuticals for oral and topical use, and it is widely used as a technological adjuvant in the drying of vegetable extracts by spray drying [25].

Table 1: Experimental matrix according to 2^{3+1} factorial design and studied responses. T: inlet temperature, F: feed rate, CSD: proportion of colloidal silicon dioxide

Run	A	B	C	T (°C)	F (ml/min)	CSD (%)
1	1	-1	1	180	4	20
2	1	1	1	180	8	20
3	1	-1	-1	180	4	10
4	-1	1	-1	160	8	10
5	-1	1	1	160	8	20
6	1	1	-1	180	8	10
7	-1	-1	-1	160	4	10
8	-1	-1	1	160	4	20
9	0	0	0	170	6	15

T: inlet temperature, F: feed rate, CSD: proportion of colloidal silicon dioxide.

Run	A	B	C	T (°C)	F (ml/min)	P (%)
1	1	-1	1	180	4	20
2	1	1	1	180	8	20
3	1	-1	-1	180	4	10
4	-1	1	-1	160	8	10
5	-1	1	1	160	8	20
6	1	1	-1	180	8	10
7	-1	-1	-1	160	4	10
8	-1	-1	1	160	4	20
9	0	0	0	170	6	15

T: inlet temperature, F: feed rate, P: the proportion of CSD®.

Quercetin content

The quercetin content was quantified by High-performance liquid chromatography (HPLC) according to the method previously validated. A calibration curve relating the peak area with quercetin concentration was built using linear regression analysis. The fitted equation (y = 56948x–6354) was linear over the range of 0.4 to 7.6 μg/ml presenting a R^2>0.999. Parameters of validation such as selectivity, linearity, detection and quantification limits (LOD and LOQ, respectively) and precision or relative standard deviation (RSD) were established [26, 27]. The LOD and LOQ were evaluated on the basis of the noise obtained with analysis of non-spiked blank samples for quercetin (n = 3). LOD and LOQ were defined as the concentration of the analytic that produced a signal-to-noise ratio of 3 and 10, respectively [26]. For the total quercetin, the LOD and LOQ were estimated by the slope and mean standard deviation of quercetin concentrations used in the standard curve [27]. The LOD for the quercetin was 0.18 μg/ml, while LOQ was 0.56 μg/ml. Results of six parallel experiments indicated that precision or RSD were all<5%.

HPLC analyses were conducted in a Shimadzu liquid chromate-graphy (Shimadzu, Kyoto, Japan) coupled with a photo diode array detector (PD-M20Avp Shimadzu), equipped with a Phenomenex (Torrance, California, USA) Luna C18 chromatographic column (4.6 mm×250 mm; 5 μm) operating at room temperature (40 °C). The mobile phase used was methanol/phosphoric acid 1% (47:53) (v/v) at a flow rate of 1.2 ml/min (isocratic flow), injection volume of 20 μl, a monitoring wavelength of 370 nm, and analysis time of 30 min. The experiments were conducted in triplicate. Data analyses were conducted in the Class-VP version 6.14 SP1 Shimadzu software.

Samples of 300 mg of dried extracts were dissolved in 5.0 ml of 1:1 (v/v) ethanol: water, and stirred with a magnetic stirrer for 10 min. Then 1 ml of hexane was added to a 1 ml sample of extract and centrifuged for 10 min. The hexane phase was ruled out and 500 μl of the resulting extract was added to 9 ml of dichloromethane and centrifuged for 10 min. Finally, 4 ml of this phase was evaporated and reconstituted in 2 ml of methanol and filtered before injection into the HPLC.

Determination of the drying process yield

Process yield (PY, % w/w), or powder recovery, was calculated immediately after the drying experiments based on the ratio of the powder mass (dry basis) collected in the flask (W) to the portion of the extract feed mass (WE) that was equivalent to the solid content of CSD added by Equation (1).

$$PY\ (\%) = \frac{W(g)}{WE(g)} . 100 \ \ldots\ldots (1)$$

Statistical analysis

The data were analyzed with the aid of the Statistic 7.0 software program (Statsoft Inc., Tulsa, OK, EUA). The results were expressed as mean±SD and coefficient of variation. The means were compared using ANOVA associated with response surface methodology. Statistical significance was established through a p-value, of which values lower than 0.05 indicate that the factor impact is significant with at least 95% confidence [28].

Accelerated stability study

The stability testing of the dry extract of *M. urundeuva* obtained in the best drying condition was conducted under a temperature of 40 °C (±2 °C),a relative humidity of 75% (±5%), and controlled by a Tecnal, B. O. D. TE-371 climate chamber (João Pessoa, Brazil) for 6 mo (29). Nine samples with approximately 3g of dried product were placed in hermetic PVC–Aluminum sachets. Quercetin analyses in three samples of the extract were performed at 0, 3 and 6 mo.

Anti-inflammatory activity

The anti-inflammatory activity of the dry extract of *M. urundeuva* (ES) obtained in the best drying condition was assessed in male Swiss mice (32±5g) using the carrageenan-induced paw edema model [30]. Paw edema was induced by injecting 0.1 ml of 1% (w/v) carrageenan suspended in either saline into sub-plantar tissues of the left hind paw of each mouse. Mice were divided into four groups, each consisting of six animals that received orally the ES dissolved in water by gavage at doses equivalent to 500 mg/kg and 2000 mg/kg of the dried vegetable drugs carefully adjusted to the quantity of dry extract, either saline and diclofenac sodium (10 mg/kg) as standard reference. After one hour, a volume of 0.1 ml of carrageenan (1% w/v) was applied in the subplantar region of the right hind paw of the animals to induce edema. The paw thickness was measured before injecting the carrageenan and after 1, 2, 3, and 4h using vernier caliper. This project was approved by the Ethics Committee on Animal Research of the Federal University of Paraíba (UFPB) (Protocol No. 0207/10) and all the animals used were from the Vivarium of the Center for Biotechnology of the UFPB. The anti-inflammatory activity was calculated as the percentage inhibition of the edema in the animals treated with extract under test in comparison to the carrageenan control group using Equation (2).

$$PY\ (\%) = \frac{To - Tt}{To} . 100 \quad .... (2)$$

Where Tt is the paw thickness of mice given the test extract at a corresponding time and To is the paw thickness of mice of the control group at the same time.

RESULTS

Evaluation of the drying parameters

Table 2 shows the results of the 2^{3+1} factorial experimental design that involved the following variables: the drying air inlet temperature, the flow rate of the drying composition fed to the spray drying, and the proportion of CSD.

Table 2: Evaluation of the drying parameters in dry extracts of *M. urundeuva* obtained by spray drier

Drying parameters (CSD/inlet temperature/feed rate)	Process yield (%)*	Quercetin (µg/ml)*
20% 160 °C 8 ml/min	37.9+0.06	20.1+0.4
20% 160 °C 4 ml/min	37.1+0.04	19.8+0.2
20% 180 °C 8 ml/min	41.2+0.06	20.8+0.2
15% 170 °C 6 ml/min	39.5+0.08	21.4+1.1
10% 180 °C 4 ml/min	40.9+0.03	23.3+1.4
20% 180 °C 4 ml/min	40.9+0.04	20.8+1.0
10% 180 °C 8 ml/min	39.1+0.07	23.0+0.7
10% 160 °C 4 ml/min	42.7+0.06	23.2+0.5
10% 160 °C 8 ml/min	44.5+0.06	21.7+0.4

* Values represent the mean±Standard deviation (n = 3/group). CSD: proportion of colloidal silicon dioxide.

Statistical analyses were performed by ANOVA and multiple linear regression using the response surface methodology to evaluate the effect of the factors on the process yield and concentration of quercetin in dry extracts of *M. urundeuva*. A significance value of $p<0.05$ was established and values lower than this were ignored. A summary of the main effects and their significance values are provided in table 3.

Fig. 1 shows the response surface of quercetin concentration in the dried extract of *M. urundeuva* as a function of the extract feed rate and inlet temperature, which are important factors in the drying process that directly influence product characteristics.

Assessing the degree of influence of these factors can help achieve greater efficiency in the drying process.

Table 3: Summary of significance (ANOVA) of the effect of the independent variables on the responses analysed in factorial design when obtaining dry extracts

Independent variables	*P-value*	
	Process yield	**Quercetin content**
Inlet Temperature	0.464907	0.000340
Feed rate	0.767776	0.006605
CSD	0.367157	0.207443
Inlet Temperature*Flow rate	0.470684	0.000285
Inlet Temperature*CSD	0.685150	0.000035
Feed rate*CSD	0.301538	0.263401
Inlet Temperature*Feed rate*CSD	0.797260	0.010428

CSD: proportion of colloidal silicon dioxide.

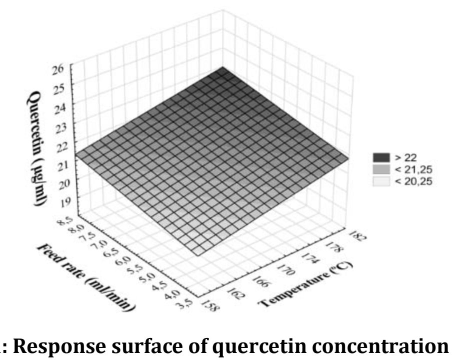

Fig. 1: Response surface of quercetin concentration in *M. urundeuva* dried extract as a function of the extract feed rate and inlet temperature

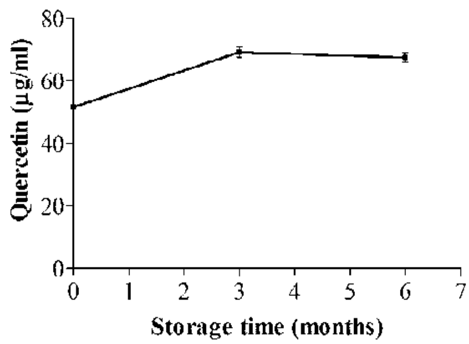

Fig. 2: Concentration of quercetin in spray dried extract stored during the stability test (n = 3/group)

Accelerated stability study

Fig. 2 shows the concentrations of quercetin in extract samples stored at 40 °C (±2 °C) and 75% (±5%) during the stability testing period of 6 mo.

Anti-inflammatory activity

Table 4 shows the results of the anti-inflammatory effect of the dry extract of *M. urundeuva* (DEMU) administered by oral route in mice evaluated by the method of paw edema induced by carrageenan.

Table 4: Effect of dry extracts of *M. urundeuva* in the paw edema induced by carrageenan in mice

Time (h)	Difference between the right and left paws (mm)				Inhibition (%)		
	CG 1%	DICLO 10 mg/kg	ES 500 mg/kg	ES 2000 mg/kg	DICLO 10 mg/kg	DEMU 500 mg/kg	DEMU 2000 mg/kg
0	0.1+0.2	0.0+0.1	0.0+0.1	0.0+0.1	-	-	-
1	1.4+0.2	0.8+0.4***	0.8+0.2***	0.4+0.4***	46.4	49.0	69.0
2	1.6+0.3	0.7+0.2***	0.7+0.3**	1.2+0.5***	59.8	60.2	26.8
3	1.2+0.3	0.6+0.2**	0.6+0.3***	1.0+0.3***	53.4	37.8	20.5
4	1.4+0.3	0.6+0.2**	0.6+0.3***	1.1+0.3***	59.3	43.9	16.0

Values represent the mean of difference of paw measure±Standard deviation (n = 6/group). Statistically different from the control group, ** p<0.01, ***P<0.001 (ANOVA followed by Student Newman-Keuls test). DEMU: Dry extract of *M. urundeuva*, DICLO: Diclofenac sodium, CG: carrageenan.

DISCUSSION

Evaluation of the drying parameters

According to table 2, the results of the 2^{3+1} factorial experimental design involving the variables drying air inlet temperature, flow rate of the drying composition fed to the spray drying, and the proportion of CSD showed that variations in these drying parameters did not result in major changes in process yield or the quercetin levels in dry extracts, but evaluating the effect and significance of these factors on the process yield and concentration of quercetin, statistical analyses were performed by ANOVA and multiple linear regression using the response surface methodology.

As shown in table 3, the independent variables (drying temperature, feed rate and proportion of CSD) did not significantly affect the process yield (p>0.05). However, the drying temperature and feed rate significantly influenced the concentration of quercetin (p ≤0.05). The analysis of the response surface of the quercetin concentration data in dry extracts showed that as the temperature was increased in association with an increase in the feed rate of input material, the concentration of quercetin also increased (fig. 1).

This indicated that at a temperature of 180 °C and a feed rate of 8 ml/min resulted in an increase in drying efficiency. During the process of drying plant extracts, the increase in temperature generally reduces the surface tension and viscosity of the input material, facilitating the formation of droplets and resulting in higher quality products [31, 32]. Proper adjustment of the feed speed enables the droplets to evaporate before they come into contact with the walls of the drying chamber, preventing the accumulation of material on the chamber walls [33, 34]. Secondary interactions were also observed between the inlet temperature and the CSD (p≤0.05), which may have occurred because the temperature variable displayed high significance and the proportion of CSD reacted, making this interaction significant. This was also found upon evaluating the tertiary interaction of the three factors that were significant (p≤0.05) due to the significant variables drying temperature and feed rate [35].

The increase of temperature and feed rate favored the concentration of quercetin in dry extracts, while the proportion of CSD had no significant influence, so the extract obtained with a 10% proportion of CSD, 180 °C inlet temperature and 8 ml/min feed rate was chosen to perform the accelerated stability study and evaluation of anti-inflammatory activity.

Accelerated stability study

An accelerated stability study was performed to better characterise the dry extract of *M. urundeuva* and monitor quercetin markers for a longer period of time. The stability of pharmaceutical products is essential for assessing the maintenance of quality and efficiency of products during the period and conditions storage, especially of plant products that are more susceptible to physical, chemical and microbiological changes.

Fig. 2 showed the concentrations of quercetin in extract samples stored at 40 °C (±2 °C) and 75% (±5%) during the stability testing period of 6 mo. There was an increase in the value of the concentration of quercetin after 3 mo (69.2 µg/ml) compared to the initial concentration (51.5 µg/ml), though this remained stable (67.4 µg/ml) after 6 mo. This may have occurred due to the evaporation of volatile components present in the extract and moisture loss resulting in increased concentration of quercetin [36].

Thus this study indicated that the drying process by spray dryer resulted in stable extracts dried relative to the preservation of their chemical constituents and the quercetin showed stable physical and chemical characteristics, making it a suitable biomarker for monitoring the studied processes.

Anti-inflammatory activity

Table 4 showed the results of the anti-inflammatory effect of the dry extract of *M. urundeuva* (ES) administered by oral route in mice evaluated by the method of paw edema induced by carrageenan. The inhibitions of the paw edemas were significantly different between the groups of diclofenac sodium and the groups that were administered two dosages of the extracts (p<0.05). At a dose of 500 mg/kg, the highest percentage of inhibition of edema was observed at 2 h, while the highest percentage of inhibition of edema was observed at one hour for a dose of 2000 mg/kg. Carrageenan is an inflammatory agent that elicits the inflammatory process and hence the formation of edema through the release of histamine, serotonin, bradykinin, and prostaglandins [3, 37-39]. Thus it is possible that compounds present in the *M. urundeuva* extract interfere with the inflammatory process mediated by these substances. Several studies have demonstrated the anti-inflammatory activity of extracts of *M. urundeuva* [3, 40-42]. This study showed the drying process by spray drier maintained chemical constituents of the extract responsible for anti-inflammatory activities of the plant.

CONCLUSION

The spray dryer technique proved to be adequate in obtaining dry extracts of *M. urundeuva* and variations in the proportion of CSD, inlet temperature, and the feed rate showed no significant variations in the drying process yield. Statistically, the study found positive a contribution to the inlet temperature and the feed rate over the concentration of quercetin on the responses analyzed, so that a 10% proportion of CSD, a 180 °C inlet temperature and an 8 ml/min feed rate was considered the most suitable condition for obtaining the dry extracts of *M. urundeuva*.

The dried extracts showed anti-inflammatory activity and the stability study indicated that the drying process by spray drying resulted in dry extracts with stable chemical constituents. In addition, the biomarker quercetin was stable during the drying process and satisfactory for monitoring and providing quality control of M. urundeuva extracts in the development of herbal products with this plant.

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CONFLICT OF INTERESTS

Declared none

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