

Spray-dried extracts from *Syzygium cumini* seeds: physicochemical and biological evaluation

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Article

Abstract: Aqueous extract from seeds of *Syzygium cumini* (L.) Skeels, Myrtaceae, obtained by dynamic maceration was spray-dried and characterized by its physicochemical and antihyperglycaemic action. The extract showed to possess high amount of polyphenols, significant *in vitro* free radical scavenger activity using the DPPH method and an antihyperglycaemic effect in alloxan-induced experimental diabetes. *S. cumini* spray-dried extracts were obtained using silicon dioxide and cassava starch as adjuvants. The powders showed acceptable flowability, compactability, and low hygroscopicity at 43% relative humidity. Besides, the spray-dried extracts showed *in vivo* antihyperglycaemic and *in vitro* scavenger activity comparable to the lyophilized extract. Thus, experimental data indicates that the extract from *S. cumini* has a relevant activity and that spray-drying could be adequately used to perform the technological processing of *S. cumini* fluid extracts.

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Introduction

Syzygium cumini (L.) Skeels (syn. *Eugenia jambolana* Lam.; Myrtaceae), is a species native from tropical Asia and well adapted in Brazil, which have been used for more than 100 years to control diabetes (Alberston et al., 2001, Helmstädter, 2008). It is also reported to be an effective antioxidant and to have anti-inflammatory and antibacterial properties (Banerjee et al., 2005, Benherlal; Arumughan, 2007, Jain et al., 2010, Kaneria et al., 2009, Pavan Kumar et al., 2010, Sari et al., 2012). It is a polyphenol-rich species and also has been reported to contain proteins and saccharides that are related to its antidiabetic effect (Ayyanar; Subash-Babu, 2012, Faria et al., 2011, Kelkar; Kaklij, 1997). Despite there are several works regarding the study of its biological activities there is none dealing with the technological processing of the extracts. Considering the increase in the use of phytomedicines worldwide and the quality and sanitary requirements regarding their production, the processing of plant extracts into standardized pharmaceutical dosage forms is not a tendency anymore but a demand to reach the phytopharmaceutical market. Similarly to conventional synthetic drugs the solid dosage forms can be considered the most convenient presentation for phytomedicines. From more than 500 plant-derived medicines registered in Brazil, nearly 70% are capsules and tablets (Carvalho et al., 2008). Considering that the majority of the raw

material for phytomedicines production consists of fluid extracts, the preparation of a solid dosage form will necessarily require a drying-step and the addition of adjuvants. Drying of plants extracts is a complex operation due to their high content of low molecular weight sugars and organic acids, which are responsible for the sticky behavior of dried products (Jaya; Das, 2009). Among several drying techniques available the spray-drying is widely used for pharmaceuticals due to adequate technological properties of dried products, short drying time as well as its high production capacity (Broadhead et al., 1992, Couto et al., 2012, Lim et al., 2011, Sarala et al., 2012). In this work the spray-drying technique was applied to process an aqueous extract from *S. cumini* and the polyphenol content, physical properties, antioxidant and antihyperglycemic activities were evaluated. The results were analysed using response surface methodology.

Material and Methods

Plant material and aqueous extract

Syzygium cumini fruits were collected at the Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Brazil. *S. cumini* trees located at the campus are identified and a voucher specimen is deposited at the SPFR Herbarium from the Biology Department of the Faculdade de Ciências e Letras de Ribeirão Preto

(Registration number: SPFR13009, Coordinates: S21°10.5994' W047°50.6279'). Seeds were removed from the fruit, oven dried at 35 °C for 48 h and grinded in a cutting mill resulting in a powder material with broad size distribution (64% smaller than 355 µm and 31% between 355 and 710 µm). Seed powder was macerated with distilled water (1:2 w/v) under magnetic stirring at 200 rpm for 12 h at 8 °C. The extract was then vacuum filtered using a Büchner funnel and paper filter resulting in an extract with a total solids content of 4.92% w/v.

Total polyphenols

Folin-Ciocalteu method was used to determine the total polyphenols using gallic acid as standard. A 50% ethanol solution was used for the preparation of standard curves and sample dilution. A volume of 0.5 mL of a 250-fold dilution of the aqueous extract and the standard curve samples ranging from 5 to 20 µg/mL were added to 0.5 mL of the Folin reagent (Merck, New Jersey, USA) and mixed with 0.5 mL of a 10% sodium carbonate solution. Samples were incubated for 1 h at room temperature prior to the spectrophotometric determination. Absorbance was determined at 710 nm. All analysis were performed in triplicate.

Flavonoids content

The aluminium chloride method was used to determine the flavonoid content using quercetin as standard. A 50% ethanol solution was used as solvent, similarly to the determination of polyphenols. Quercetin standards prepared from 1 to 25 µg/mL and a 5-fold dilution of the aqueous extract were added to 0.5 mL of a 2% aluminium chloride solution. Samples were incubated for 1 h at room temperature and the absorbance was measured at 420 nm. All analysis were performed in triplicate.

Drying methodologies

Screening of adjuvants

A screening of suitable adjuvants including maltodextrin Mo-rex 1920 (Corn Products, São Paulo, Brazil), corn starch (Henrifarma, São Paulo, Brazil), microcrystalline cellulose (Henrifarma, São Paulo, Brazil), silicon dioxide (Aerosil 200, Evonik, Essen, Germany), polyvinylpyrrolidone (Kollidon 30, Basf, Ludwigshafen, Germany) and cassava starch (Flo-max®, National Starch, New Jersey, USA) was performed by mixing the aqueous fluid extract with each adjuvant for 15 min using magnetic stirring. The total solid content of the extract added with adjuvants was fixed at 10%.

The mixture was oven-dried in petry dishes at 70 °C for 1 h. Those who could be easily removed from plates using a spatula were evaluated for spray-drying of the aqueous extract.

Spray-drying

The spray-drying process was studied in a bench scale apparatus (MSD 1.0 Labmaq do Brasil, São Paulo, Brazil) having a two-fluid nozzle, a drying chamber having 50 cm of high and an internal diameter of 15 cm. The following operational parameters were used: 130 °C and 60 °C of inlet and outlet temperatures respectively, atomizing pressure of 2 kgf/cm², air rate of 50 scfh and suspension feed of 5 mL/min. Lyophilization was performed for 36 h in a 10-145-MR-BA Virtis equipment (Sp Scientific, New York, USA) without the use of adjuvants. Spray-dried and Lyophilized extracts were coded as SDE and LDE, respectively.

Experimental design

A 2³ experimental design was applied for the drying study using two adjuvants selected in the initial screening. Also, the extract:adjuvant ratio and the time of adjuvant incorporation were evaluated. Table 1 shows the matrix of the experimental design and Table 2 the factors and levels studied.

Table 1. Matrix of the experimental design.

Experiment	Coded Variables		
	X ₁	X ₂	X ₃
1	-1	-1	-1
2	-1	-1	+1
3	-1	+1	-1
4	-1	+1	+1
5	+1	-1	-1
6	+1	-1	+1
7	+1	+1	-1
8	+1	+1	+1

Table 2. Levels of the factors in the experimental design applied on the drying study.

Factor	Level	
	-1	+1
ADJ	Aerosil	Cassava Starch
E:A (g/g)	1:5	1:8
TI (h)	0.25	3

*ADJ: adjuvant; E:A: Extract: adjuvant proportion; TI: Time of incorporation.

Physicochemical characterization

Physicochemical properties of the SDE including bulk and tapped densities, residual moisture content, Hausner ratio, particle size, angle of repose and hygroscopicity were evaluated as follows:

- Tapped (ρ_T) and Bulk density (ρ_B) determinations were performed using a 10 mL graduated cylinder. To the former determination an electromagnetic sieve shaker was adapted to allow an efficient and reproducible level of tapping. The materials were tapped until constant volume.

- Hausner ratio (Hr) is the ratio between the tapped and the loose-packed bulk densities of the powder (Thalberg et al., 2004) and it gives indication of the compressibility properties of the materials.

- A halogen moisture analyzer (Ohaus, MB 45, New Jersey, USA) was used to determine the residual water content (W) of each extract. The values were expressed in percentage of water on dry basis.

- The particle diameter (dp) evaluation was performed by optical microscopy and image capture. The images were obtained using a LQT3 microscope (Lambda, Harpenden, UKA) connected to a digital CCD camera (Samsung SCC 131, New Jersey, USA) and a PC computer with image capture board DC10-Plus (Pinnacle Co., California, USA). The images of at least 1000 particles of each sample were analyzed using the software Image J (National Institute of Health v.1.31)

- Angle of repose (α_r) was measured using a Petri dish according to Brown & Richards (1970). The half full Petri dish, inclined at an angle of 90° was smoothly rotated by hand until the surface powder exhibits its maximum angle, which is considered to be the angle of repose. The result is an average of ten measurements.

- To determine the hygroscopicity the dried extracts were exposed to relative humidities (RH) of 43 and 90% using saturated salt solutions of zinc sulphate and potassium carbonate, respectively, during seven days. These solutions were kept under controlled temperature and the water uptake was determined gravimetrically with two replicates of each extract.

After the technological characterization, one spray-dried extract was chosen to perform the *in vitro* and *in vivo* biological assays. The activities were compared to the lyophilized dried extract.

In vitro free radical scavenging activity

The antioxidant activity of the dried extracts was evaluated using the free radical 1,1-diphenyl-2-picryl-hydrazyl (DPPH). Ethanol solutions of the LDE and SDE ranging in concentration from 2.5 to 22.5 $\mu\text{g/mL}$ were compared. A volume of 50 μL of sample

(or ethanol as control) was added to 1 mL of ethanol, 1 mL of a 0.1 M acetate buffer (pH 5.5) and 0.5 mL of a 250 μM DPPH solution in ethanol. Measurements of DPPH free radical absorbance were performed at 510 nm after 10 min of incubation at 25 $^\circ\text{C}$. Samples scavenging activity was calculate as the DPPH free radical inhibition percentage. Results were expressed as the sample concentration able to reduce in 50% the amount of DPPH free radical (IC50).

Evaluation of the antidiabetic effect

Male adults Wistar rats weighting 200 ± 20 g were obtained from the Central Experimental Animal (CEA) facility from the University of São Paulo, Ribeirão Preto, Brazil and kept at 23 ± 2 $^\circ\text{C}$ in groups of five normal or three diabetic animals under 12 h light and 12 h dark cycles with free access to water and food. For induction of diabetes animals were administered with an intravenous injection of a 35 mg/kg alloxan solution (Sigma, Missouri, USA) in citrate buffer pH 4.5 after 48 h of fasting. On the fourth day post-injection animals were fasted for 12 h and anesthetized with a 1:1 ketamine and xilazine solution at 0.75 $\mu\text{L/g}$. Glucose level in serum was determined using a commercial kit (Glicose HK Liquiform, Labtest, Minas Gerais, Brazil). Animals with glucose levels higher than 200 mg/dL where further used in the experiments. All procedures were approved by the University Committee on animal experimentation (File 04.1.1151.53.9). Animals were divided in groups of 7 to 10 as follows: a non-diabetic untreated control group and four diabetic groups (untreated control, treated with LDE, treated with SDE and treated with silicon dioxide only). The extracts were given at a daily dose of 200 mg/g of body weight.

Statistical analysis

Data from the experimental design were analyzed by multiple linear regression using the module Visual General Linear Model (VGLM) of the software Statistica 7 (Statsoft, Inc., Oklahoma, USA). To evaluate the homogeneity of serum glucose from rats before the treatment, one-way ANOVA followed by Newman-Keuls test was performed using Prism 3.0 GraphPa software (GraphPad, California, USA). The antidiabetic effect was analyzed using paired t-test comparing serum glucose before and after treatment, for each group separately using the software Excel (Microsoft Inc., Washington, USA).

Results and Discussion

Total phenolic content of the aqueous extract showed to be 143.3 ± 2.1 mg/g of plant material; which gives a value of 14.35% of phenolics on dried seeds of *S. cumini*. For comparison, the total polyphenol content in methanolic and aqueous fractions of *S. cumini* leaves was found to be 180 and 94 mg/g, respectively, using the Folin-Ciocalteu and acid gallic as standard (Kanerla et al., 2009). An infusion made from the skin of the ripe fruits of *S. cumini* showed the presence of around 100 mg/g of phenolics (Banerjee et al., 2005). Benherlal & Arumughan (2007) compared the total phenolic content of ethanolic extracts from pulp, seed and seed coat using a similar method. The seeds presented the highest amount of phenolics (370 mg/g). Thus, many parts of *S. cumini* including seeds have a significant polyphenolic content and the antioxidant properties of these compounds are frequently associate to the antidiabetic effect of many plant species (Hanamura et al., 2005, Sabu et al., 2002).

The flavonoid content was 1.4 ± 0.008 mg/g in the dried seeds. The ethanolic extract of pulp and seeds presented 30 and 25.30 mg/g of flavonoids (Benherlal; Arumughan, 2007) which was higher than the values in this work. In the case of leaves it was found that flavonoids represent the main group of phenolics in the methanolic extract (Ruan et al., 2008); however it is not the case of the extract obtained herein. Besides the flavonoids other compounds such as phenolic acids, anthocianins and tannins may be related to the antioxidant activity, and they were already described to be found in this species (Ayyanar; Subash-Babu, 2012, Faria et al., 2011, Sah; Verma, 2011).

The IC₅₀ DPPH scavenger activity of the LDE was of 9.99 µg/mL which can be considered a very significant activity. Ethanolic extracts of pulp, seed and seed coat showed values of IC₅₀ of 158.0, 8.6 and 48.0 µg/mL, respectively (Benherlal; Arumughan, 2007). Hence, the seeds seemed to be the fruits part with the

most prominent antioxidant potential, comparable to vitamin C, which is of around 7.0 µg/mL (Benherlal; Arumughan, 2007). The methanolic leaf extract showed a IC₅₀ of 125 µg/mL (Ruan et al., 2008).

In regard to the antidiabetic effect of *S. cumini*, some of the compounds to whom its biological effect is ascribed are glycoproteins and oligosaccharidess (Kelkar; Kaklij, 1997), which are more thermosensitive than most of plants secondary metabolites. Considering that there was an indication of the occurrence of at least one of these compounds in the seeds aqueous extract studied herein (Peixoto, 2005) and that this work aimed to evaluate the influence of the spray-drying on the physicochemical and biological properties of extract, no other step involving the use of heat was used. Then, after filtration the technological adjuvants were added to the extract and submitted to the drying process.

In many cases, quality assurance of phytopharmaceutical products is focused solely on its chemical and biological properties. However, the physical behavior plays a key role for the manufacturing, processing and stability of plant extracts and can be related to pharmacological properties either (Crippa, 1978, Endale et al., 2004, List & Schmidt, 1989). Table 3 presents the results of physicochemical properties of the spray-dried extracts.

Bulk densities varied from 0.181 to 0.321 which are considered low values of unpacked density. Although usual for plant dried extracts, it may be considered a limitation for tableting by direct compression, which is the technique of choice for the manufacture of thermolabile and moisture-sensitive products, in addition to its economic advantage (Jivraj et al., 2000). Wanczinsky et al. (2002) reported bulk densities from 0.72 to 0.83 g/mL for powders used in direct compression process.

The Hausner ratio is a measure of interparticle friction and has been widely used as an indication of the compaction properties of materials. According to Wanczinsky et al. (2002) hausner ratios less than 1.25

Table 3. Physicochemical properties of the spray-dried extracts obtained using the adjuvants cassava starch and silicon dioxide.

Exp.1	Var. 1	Var. 2	Var. 3	ρB (g/mL)	ρT (g/mL)	Hr	αr	W	Ps
1	CS	1:5	0.25	0.321	0.465	1.45	57.0	5.95	15.60
2	CS	1:5	3	0.265	0.353	1.33	52.0	6.75	12.23
3	CS	1:8	0.25	0.242	0.459	1.89	59.8	5.56	10.87
4	CS	1:8	3	0.221	0.336	1.52	52.4	9.85	10.02
5	SD	1:5	0.25	0.181	0.218	1.20	53.0	3.92	11.94
6	SD	1:5	3	0.213	0.246	1.16	55.6	4.29	17.15
7	SD	1:8	0.25	0.198	0.227	1.15	54.4	4.28	16.89
8	SD	1:8	3	0.224	0.238	1.06	50.6	4.03	15.68

*Exp: experiment; CS: Cassava starch; SD: Silicon dioxide; Var.1: adjuvant type; Var. 2: extract adjuvant:proportion; Var.3: time of incorporation; ρB: bulk density; ρT: tapped density; Hr: hausner ratio; αr: angle of repose; W: residual humidity; Ps: particle size.

are related to a better degree of compaction. The higher hausner ratios observed in the extracts using cassava starch are probably related to the formation of agglomerates.

The values of angle of repose depends on the magnitude of the friction and of the adhesion forces between particles (Alavi; Caussat, 2005). All values of angle of repose obtained indicate cohesive and very cohesive powders with very low flow properties.

For particle sizes it is generally considered that powders with sizes larger than 200 μm are free flowing, while smaller powders are subject to cohesion and their flowability is more difficult (Kim et al., 2005). The average particle diameter of spray-dried powders varied from 10.02 to 17.15 μm which agrees with the low flow properties described by angle of repose. Thus, for the production of uniform dosage forms such as tablets and capsules, a granulation step would probably be required.

The residual moisture content recommended for dried extracts is generally limited to 5%, although materials that are not hermetically sealed during storage are allowed to reach 6-7% (List & Schmidt, 1989). The spray-dried extracts are in good agreement with this requirement except extract number four. Silicon dioxide SDE presented the lowest values of residual moisture.

The statistical analysis of the influence of the type of adjuvant (categorical variable) showed significant influence on tapped density and Hausner ration with levels of significance of 1 and 5% respectively. There was no significant interaction of this variable with other factors. Results from the influence of the continuous variables (extract:adjuvant proportion and time of incorporation) indicated that the time of adjuvant incorporation influenced tapped density at 5%, according to equation 1 ($R^2: 0.9978$). Surface plot (Figure 1) shows that lower values of tapped density occurred at lower times of incorporation.

$$\rho_T \left(\frac{\text{g}}{\text{mL}} \right) = 0.40 - 0.06 \left(\frac{t - 1.625}{1.375} \right) \quad [1]$$

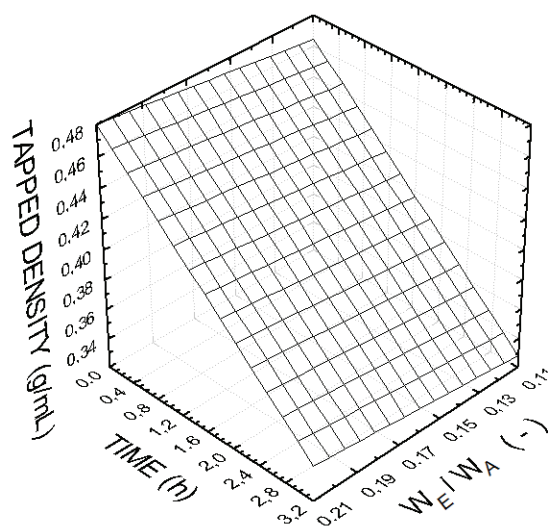


Figure 1. Response surface for tapped density as a function of time of incorporation (h) and the ratio of extract flow (W_E) and air flow (W_A).

Moisture uptake was studied at 43 and 90% of relative humidity (RH). At 43% RH the extracts analyzed presented residual moisture varying from 0 to 0.80% after 7 days which can be considered low and satisfactory. Figures 2 and 3 shows the moisture uptake at 90% RH for SDE with cassava starch and silicon dioxide. At higher values of RH extracts did not present the same behavior being the silicon-dioxide more absorptive than cassava starch. The higher water content can be related to the silicon dioxide characteristics of water sorption since this material can absorb nearly 10 times its weight in contact with moisture. In this

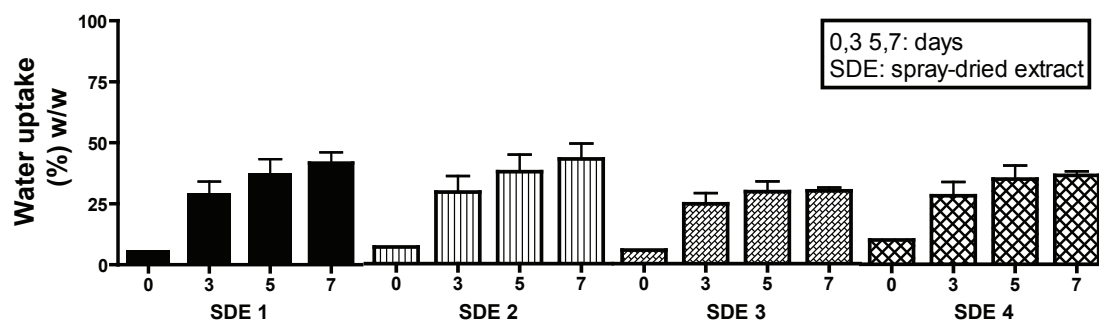


Figure 2. Moisture uptake of the cassava starch spray-dried extract (SDE) exposed to 90% RH atmosphere.

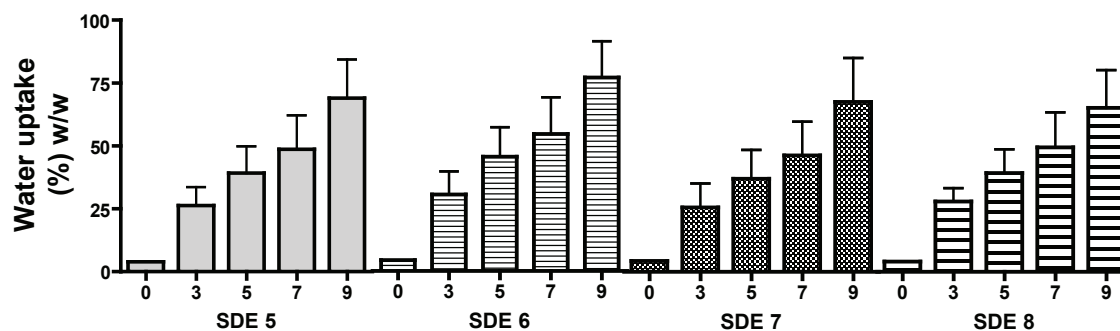


Figure 3. Moisture uptake of the silicon dioxide spray-dried extract (SDE) exposed to 90% RH atmosphere.

sense depending on the ambient conditions and the application of the extract (e.g. if it will be used for capsule filling without the incorporation of some other adjuvants) selection of drying adjuvants should be carefully performed.

Petrovick et al. (2010) obtained spray-dried extracts from *Achyrocline satureioides* (Lam.) hydroethanolic extracts using silicon dioxide as adjuvant. Physical evaluation showed indication of poor flowability and compactability. Hausner ratio and particle size were very similar to the data obtained here although higher values of angle of repose were obtained for dried extracts of *S. cumini* indicating probably a higher degree of agglomeration for this last one. Granulation of spray-dried extracts of *A. satureioides* was able to improve physical properties of the powder and also has diminished the moisture absorption at higher values of RH, which allows further formulation of the powder.

Despite the higher absorptive behavior of the silicon dioxide extracts, the better physical properties such as hausner ratio, residual humidity and the less agglomerative feature prompted us to select the dried extract added to silicon dioxide at the 1:5 proportion and 0.25 h of incorporation to perform the biological evaluation. Because of the absence of significance of variable 2 the lower proportion of adjuvant was preferred.

Regarding *S. cumini* application, the IC₅₀ of the lyophilized and spray-dried extracts were 9.99 and 10.74 µg/mL respectively which gives indication that with both processes is possible to obtain the same level of antioxidant activity. For the antidiabetic effect the same was observed (Figure 4).

However, none of the extracts were able to lower blood glucose levels. It was observed an antihyperglycaemic effect since the values of glucose were stabilized with the LDE and SDE treatment. Glucose of untreated diabetic groups increased with time. As expected, animals treated only with the drying adjuvant showed the same profile as the untreated diabetic group.

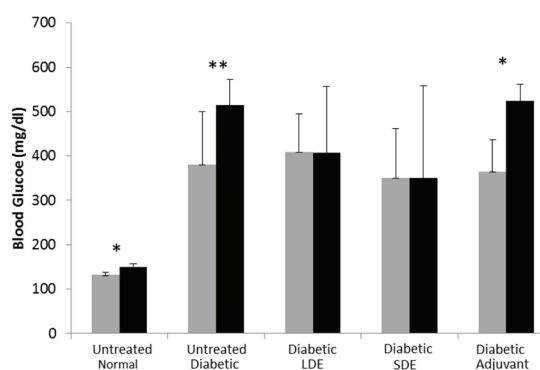


Figure 4. Comparison of the antidiabetic effect of spray-dried (SDE) and lyophilized extract (LDE). Blood glucose levels is showed before treatment (grey bars) and after 21 days of treatment (black bars). Significances for the paired T-test: *1%, **5%.

Conclusion

An aqueous extract was obtained from seeds of *Syzygium cumini* which showed to be rich in polyphenols and to possess a significant *in vitro* antioxidant effect. For the drying of the extract two adjuvants were considered suitable: cassava starch and silicon dioxide. Spray-dried extracts using these adjuvants separately presented low flowability, low compactability and hygroscopicity at high relative humidity, which will probably require the use of granulation process to produce solid dosage forms. Nevertheless, the extracts showed antihyperglycaemic and *in vitro* antioxidant activity comparable to the lyophilized extract which indicates that for the activities proposed the spray-drying technique showed little influence upon the active compounds of the extract. Data showed here indicates that the extract from *S. cumini* showed a relevant activity and that the spray-drying is a technique that could be adequately used to perform the technological processing of *S. cumini* fluid extract.

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