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Lipase-mediated alcoholysis for *in situ* production of ester bioaromas in licuri oil for cosmetic applications

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ABSTRACT

Bioaromas can be produced by lipases either through their hydrolytic or (trans)esterifying activities. Therefore, this work reports the development of a lipase-catalyzed biotransformed licuri oil, forming volatile ethyl esters with odor notes resembling tropical fruits. Ethyl octanoate formation was promoted when 7.0 % (m/v) Lipozyme 435® was used to convert a grain alcohol:licuri oil mixture (51:49, v/v) at 58ºC and 70 rpm for 6 hours. The biotransformed oil has shown antimicrobial activity against *Staphylococcus hominis*, *S. epidermidis,* and *Corynebacterium xerosis*, bacteria associated with bad skin odor. Finally, this biotransformed oil was used without further treatments (e.g., recovery or purification procedures) to prepare two cosmetic formulations (in a dosage of 1.5 %), aiming for both fragrant and deodorant activity.

1. Introduction

In 2022, the global market for flavors and fragrances reached USD 29.27 billion. Projections suggest that it is poised to grow to approximately USD 48.82 billion by 2032, reflecting a CAGR of 5.3 % during the forecast period from 2023 to 2032. One of the factors associated with the expansion in the market is the increasing innovation in the cosmetic sector and the ever-increasing demand for natural flavors and fragrances (Precedence Research, 2023). In turn, the market for biotechnological flavors (also called bioaromas), whether by microbial fermentation or enzymatic reactions, valued at US$ 1.54 million in 2021, is projected to grow at a CAGR of 11.0 % from 2021 to 2028, reaching US$ 3.17 million. Market growth is driven by adverse weather conditions and increasing demand for high-quality food ingredients. However, the high cost associated with processing, producing, and preserving natural and biotech flavors is projected to hinder market growth, as biotech flavors are comparatively more expensive than synthetic alternatives (COHERENT Market Insights, 2021).

The high production costs of bioaromas come mainly from the purification stage of the produced compounds, accounting for more than 50 % of the cost of the bioprocess (Intasian et al., 2021) due to the high volatility of the aroma molecules and their low solubility in green solvents. In addition to being financially costly, the downstream stage in the production of bioaromas is complex and leads to low yields (Sharma et al., 2020). An alternative to reduce costs in producing bioaromas is using agricultural by-products, which meets consumers' desire for more sustainable, natural, and environmentally friendly products (Paulino et al., 2021; Singh et al., 2024).

Lipases (glycerol ester hydrolase E.C. 3.1.1.3) are enzymes typically involved in the hydrolysis of triacylglycerols (TAG) of oils and fats, which can be used to produce bioaromas (e.g., cheese flavoring short-chain fatty acids) (Barron et al., 2004; Vélez et al., 2023). Apart from hydrolysis reactions, lipases can also catalyze esterification and transesterification reactions at specific conditions. This can also lead to the production of volatile odor-active esters by reaction between low molecular mass alcohols (e.g., ethanol) and oils composed of short-chain fatty acids (Abeijón Mukdsi et al., 2018). Among the advantages of this reaction system are the mild process conditions, the short reaction time, the possibility of reuse of the enzyme, and the occurrence of the reaction in solvent-free lipophilic systems, as long as there is a layer of hydration at the enzymatic active site. This technology can generate esters that, apart from their odor properties, may also act as emollients, emulsifiers, and lubricants (Vilas Bôas et al., 2022).

Syagrus coronata (Arecaceae), popularly known as licuri palm, is an endemic species of the Brazilian Caatinga that has ecological and socioeconomic significance due to the high content of oil and protein present in the seed of its fruit (Neves et al., 2023). Licuri oil has a higher amount of saturated fatty acid (around 90 %), with a great abundance of

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lauric acid (43–48 %) and myristic acid (around 14 %). Oleic acid (7–12 %), octanoic acid (10–13 %), and decanoic acid (6–8 %) also feature prominently (dos Santos Souza et al., 2021; Iha et al., 2014). The presence of lauric acid in high concentrations gives licuri oil lipophilic adjuvant and moisturizing properties, being compared to oils traditionally used in cosmetic products, such as coconut, sweet almond, and palm kernel oil (Lisboa et al., 2020). Since it is rich in short and medium saturated chains, licuri oil has low viscosity and is relatively stable to oxidation (Iha et al., 2014). Moreover, as previously mentioned, this oil can be used as a starting point for producing volatile esters using the transesterification activity of lipases.

The biological properties of licuri oil also involve antimicrobial actions against *S. aureus*, including methicillin-resistant strains (Cibele et al., 2016; De Lacerda Coriolano et al., 2021), and larvicidal (action of capric and lauric acids) and oviposition-deterrent (action of caprylic acid) activities against *Aedes aegypti* (Santos et al., 2017). In oral toxicology, mutagenicity, and carcinogenicity tests, with single-dose administration of licuri oil of 2000 mg/kg body weight in mice, no adverse effects were observed in the animals. In acute toxicology tests, there were no changes in the liver, kidneys, and spleen (dos Santos Souza et al., 2021).

Given the above, some cosmetic companies, such as L'Occitane, already use licuri oil in their products, such as body deodorant oil, liquid soap, and moisturizing body cream gel, with claims of antioxidant properties and formation of an anti-pollution barrier (L'Occitane au Brésil, 2023). This work aimed to go further and to produce licuri oil enriched in odor-active ethyl esters of short-chain fatty acids by biotransforming this oil, while using this lipase-biotransformed licuri oil in cosmetic formulations with any downstream processing. Therefore, besides the technological and biological properties already mentioned (associated with the unreacted oil components), this biotransformed oil would present volatile esters impairing fruity odors, which could replace the use of fragrant ingredients in that formulation without any prior recovery or purification of the odorizing molecules. Moreover, this study intended to test the antimicrobial effect of the biotransformed licuri oil on bacteria responsible for the appearance of foul odor on the skin, thus impairing a potential deodorant property to the final product.

2. Materials and methods

2.1. Enzyme and chemicals

Licuri oil (Bottica Botanika), grain alcohol (Synth), and the enzyme ("Lipozyme® 435 for oleochemicals | Novozymes," n.d.). were used for the esterification reaction. For the analytical determinations, the following were used: absolute ethanol (99.5 % v/v) HPLC grade (Dinâmica), potassium hydroxide (Synth), phenolphthalein (Anidrol), isopropyl alcohol (Anidrol), oleic acid (Dinâmica), and resazurin sodium salt (Sigma-Aldrich). Ethyl octanoate (Sigma-Aldrich) and ethyl laurate (Sigma-Aldrich) were used as analytical standards. For the formulation of the moisturizers, the following were used: the non-ionic self--emulsifying wax UNIOX-C (cetearyl alcohol and polysorbate 60, kindly donated by CHEMYUNION), ZEMEA propanediol (SARFAM), ProTeg SL (Proserv Química), EDTA (Dinâmica), and anhydrous citric acid (Química moderna).

2.2. Strains and media

For the microbiological assays, strains of *Staphylococcus hominis* subsp. hominis ATCC 27844 (Coleção de Culturas Tropical – Fundação André Tosello), *Staphylococcus epidermidis* (Winslow and Winslow) Evans, and *Corynebacterium xerosis* Lehmann and Neumann were used. The strains were grown in Triptone Soy Broth (Kasvi) at 37ºC and maintained on nutrient agar (Neogen Culture Media) at 30ºC, being chopped weekly.

2.3. Esterification reactions

The esterification reactions occurred in a solvent-free system in 250 mL Erlenmeyers stirred in a Dubnoff water bath with orbital agitation (TECNAL TE-0532) at 70 rpm/min. The reaction volume was fixed at 5 mL, comprising a mixture of licuri oil, grain alcohol, and enzyme. The volumetric percentage of each reagent, the mass percentage of lipase, and the temperature of each test followed the experimental designs presented in item 2.4. The time of each reaction was set at six hours. Since then, no significant sensory changes have been noticed afterward.

2.4. Evaluation of the main parameters involved in licuri oil biotransformation for bioaroma production

Following the procedure described before (Section 2.3), two Central Composite Rotatable Designs (CCRD) were used to evaluate the effect of the main parameters involved in producing ethyl octanoate by the transesterification reaction. The first was a 2^3 factorial design with six trials at the axial conditions and three repetitions at the central point, totaling 17 trials, varying the lipase concentrations (0–10 %, given mass of lipase per total reaction volume), the percentage of grain alcohol in the reaction mixture (9.10–60.40 %, given as volume of grain alcohol divided by the volume of grain alcohol plus volume of licuri oil) and the temperature of the reaction (53.2–86.8ºC). The second was a 2^2 factorial design with four trials at the axial conditions and three repetitions at the central point, totaling 11 trials, varying the percentage of grain alcohol (50.90–79.10 %) and the temperature of the reaction (36.9–58.1ºC) (Rodrigues and Iemma, 2014).

From the results, second-order models were obtained and evaluated statistically by analysis of variance (ANOVA) using the software Protimiza Experimental Design ("Protimiza Experimental Design," n.d.). The results were analyzed for differences between means by Student t-test ($p < 0.05$). The model validation was performed under the ideal conditions indicated by the equations.

2.5. Analysis of volatiles

To obtain the ester profile in the biotransformed licuri oil, the sample was previously diluted in ethanol (1:1000) and vortexed (IKA, MS 3 digital) for 60 s. 1 μL of the sample was injected into the gas chromatograph coupled to the mass spectrometer (GC–MS, Agilent 7820 A GC system and 5977E insert MSD, Santa Clara, CA, USA). An HP-5-MS column (30 m long, 0.25 mm internal diameter, and 0.25 μm film thickness) was used. The oven temperature started at 80 °C and was maintained for 2 min, being raised at a rate of 20 °C.min^{-1} until reaching 280 °C, at which temperature it was maintained for 2 min. The carrier gas used was helium, at a flow rate of 1 mL.min^{-1}. The injector temperature was 250 °C in split mode (1:20) (Bicas et al., 2008). The detector was maintained at 250 °C in the transfer line, with electron ionization at + 70 eV, working with a mass range of 35–450 *m/z*. The solvent delay time was 3.50 minutes. The compounds were identified by

comparison with the NIST2014 library and also based on their retention indexes, calculated as Eq. 1 ("The IUPAC Compendium of Chemical Terminology," 2019):

$$RI = 100 * \left(\frac{t_c - t_n}{t_{n+1} - t_n} + n \right) \quad (1)$$

t_c is the retention time of the compound of interest, t_{n+1} is the retention time of the subsequent hydrocarbon; n is the number of carbons of the previous hydrocarbon.

For the quantitative analyses of the esters present in the biotransformed licuri oil, the same chromatographic methodology described above was followed in a Gas Chromatograph coupled with a Flame Ionization Detector (GC-FID, Agilent 7890 A) and an HP-5 column (30 m long, 0.25 mm internal diameter, and 0.25 μm film thickness). In this case, the samples were diluted 1:10 (v/v) in ethanol, and the injector was set to split mode (1:10). Quantification was performed using a standard curve involving ethyl octanoate (Sigma-Aldrich) and ethyl laurate (Sigma-Aldrich), with 2-heptanol as the internal standard. The other esters generated were semi-quantified based on the calibration curve of ethyl octanoate.

For the analysis of formulated moisturizers, a total of 1.0 g of each sample was put in a 10 mL bottle sealed by a cap with polytetrafluoroethylene septum (PTFE) and placed in a thermostatic bath (Lauda Alpha RA8, Lauda-Königshofen, Germany) at 50ºC. After 5 min, volatile compounds were extracted using the solid phase microextraction (SPME) technique with a holder (Sigma–Aldrich 57330) equipped with a DVB/CAR/PDMS (divinylbenzene/carboxen/polydimethylsiloxane, 50/30 μm) fiber. The microfiber exposure time was 3 min. The microfiber was immediately desorbed for 3 min in the injector port of the gas chromatograph in splitless mode.

2.6. Esterification activity of lipase

The esterification activity of Lipozyme® 435 was determined by the method proposed by Oliveira et al. (2006) with adaptations. An esterification reaction of oleic acid (Synth) with isopropyl alcohol (Synth) was performed in triplicate in a molar ratio of 3:1, in solvent-free medium, with a reaction volume fixed at 1 mL and enzyme concentration in relation to the substrates of 5 % (w/w). The system was maintained at 50 °C in a Dubnoff water bath with orbital agitation (TECNAL TE-0532) at 70 rpm for 30 minutes. The oleic acid content of samples that did not undergo reaction and of samples after reaction was determined by titration with 0.2 M KOH solution in ethanol and phenolphthalein as indicator. A unit of activity was defined as the consumption of 1 micromole of oleic acid per minute per gram of enzyme, and the activity U was calculated according to Eq. 2:

$$U = \frac{N_{OC}}{\theta M_E} \quad (2)$$

N_{OC} is the number of micromoles of oleic acid consumed in the reaction, θ is the reaction time, and M_E is the enzyme mass in grams.

2.7. Enzyme reuse

The enzyme reuse tests were performed following the protocol adopted in item 2.3. The reaction volume was fixed at 10 mL, comprising a mixture of licuri oil, grain alcohol, and enzyme. The reaction parameters followed the results from the CCRD experiment (item 3.2), and the enzyme reuse was tested five times. Between one test and another, the lipase was washed three times with grain alcohol and dried at 50ºC.

Table 1
Moisturizer formulations.

Moisturizing cream			
Formulation 1		**Formulation 2**	
Ingredient	**%**	**Ingredient**	**%**
Uniox-C	12	Uniox-C	12
ZEMEA Propanediol	3	ZEMEA Propanediol	3
PROTEG SL	0.5	PROTEG SL	0.5
EDTA	0.1	EDTA	0.1
Biotransformed licuri oil (bioaroma)	1	Biotransformed licuri oil (bioaroma)	1.5
Water	83.4	Water	82.9

Moisturizing tonic			
Formulation 1		**Formulation 2**	
Ingredient	**%**	**Ingredient**	**%**
ZEMEA Propanediol	3	ZEMEA Propanediol	3
PROTEG SL	0.5	PROTEG SL	0.5
EDTA	0.1	EDTA	0.1
Biotransformed licuri oil (bioaroma)	1	Biotransformed licuri oil (bioaroma)	1.5
Water	95.4	Water	94.9

2.8. Formulation of moisturizers

The biotransformed licuri oil was applied in four cosmetic formulations: two moisturizing creams and two moisturizing tonics, as shown in Table 1. The formulations are free of parabens, silicone, sulfate, mineral oil, dye, and essences.

The aqueous and oily phases were weighed for the moisturizing cream, and both were heated up to 75ºC. Upon reaching this temperature, the aqueous content was poured over the oily. The mixture was stirred for 20 minutes at 1000 rpm in a Fisatom 715 W mechanical agitator with a centrifugal propeller until its complete homogenization and cooling. After this time, the preservative and bioaroma were added.

The ingredients were mixed for 5 minutes at 1000 rpm for the tonic in a Fisatom 715 W mechanical agitator with a centrifugal propeller until homogenization. During homogenization, the pH of the solution was adjusted in the range of 4.0–4.5 with citric acid. After this time, the preservative and biotransformed licuri oil (bioaroma) were added.

All formulations were transferred to 10 mL glass vials sealed by a metal cap with a polytetrafluoroethylene (PTFE) septum and stored for stability analysis, as commented in item 2.9.

2.9. Stability of moisturizing formulations

For stability analysis, sacrificial samples of the moisturizing formulations were stored at different temperatures (5, 25, and 40ºC) in the dark. The stability analyses consisted of pH measurement, observation of visual fungal growth and color change, observation of phase separation, and volatiles. For the phase separation test, aliquots of the moisturizing cream samples were submitted to centrifuge tests in a centrifuge (FANEM Baby Centrifuge 206) at 3600 rpm for 20 minutes. SPME performed the volatiles analyses according to the protocol presented in item 2.5. The samples were monitored for 60 days.

2.10. Antimicrobial effect of the biotransformed licuri oil

Minimum inhibitory concentration (MIC) analyses against *Staphylococcus hominis* subsp. *hominis* ATCC 27844 (Coleção de Culturas Tropical – Fundação André Tosello), *Staphylococcus epidermidis* ATCC 12228, and *Corynebacterium xerosis* ATCC 373 were performed using the 96-well plate broth microdilution method recommended by the Clinical and Laboratory Standards Institute (CLSI, 2018) with modifications. For the analysis, nutrient broth (Neogen Culture Media) supplemented with 5 % of Tween 80 and varied concentrations of biotransformed licuri oil (10 concentrations of a serial dilution, concentrations ranging from 10 % to 0.00195 %) was used. The bacterial strains were grown for 24 hours on nutrient agar at 30ºC and standardized in nutrient broth to 10^7 CFU/mL. The inoculum (20 µL) was added to all wells containing diluted biotransformed licuri oil and to the positive control column, standardized at 10^5 CFU/mL. Negative control was also done for each plate, in which only the culture medium was added. The plates were incubated at 30 °C for 48 h. MIC is defined as the lowest concentration of the sample that inhibited visible growth, as indicated by resazurin staining (Sigma-Aldrich).

To determine the minimum bactericidal concentration (MBC), 10 µL of the lowest dilutions resulting in lack of bacterial growth in the MIC test were transferred into a Petri dish with nutrient agar. The plates were incubated at 30°C for 72 hours. MBC was considered the lowest biotransformed licuri oil concentration, resulting in no bacterial growth on the agar plate. The analysis was performed in triplicate, and non-biotransformed licuri oil was also tested in this assay (as a control).

3. Results and discussion

3.1. Occurrence of esterification reactions

Lipozyme® 435 is a nonspecific, immobilized, and food-grade *Candida antarctica* lipase B, which works at mild temperatures and can be used for a wide variety of oils, bringing benefits such as color preservation and no generation of unwanted by-products ("Lipozyme® 435 for oleochemicals | Novozymes," n.d.). It is currently used in esterification or transesterification reactions for producing odor-active esters (Ortega-Requena et al., 2024). Therefore, this enzyme was chosen to catalyze the intended alcoholysis reaction between ethanol and licuri oil, as described next.

First, the esterification activity of Lipozyme® 435 was determined in a model system comprising oleic acid and isopropyl alcohol. The results indicated an esterification activity of 530.54 µmols of oleic acid consumed/minute/gram of enzyme (data shown in Supplementary Table S1). Subsequently, a first lipase catalyzed the transesterification reaction between ethanol and licuri oil (1 % lipase and 50 % grain alcohol at 70°C) was done to check which compounds would be formed. In this case, the GC-MS analysis revealed the formation of six esters (Table 2), which are present in negligible concentrations in the enzyme-free control experiment (data shown in Section 3.2., trial 9 in Table 3).

The alcoholysis reactions between ethanol and the triacylglycerols in licuri oil could explain the formed ethyl esters. The abundance of each compound reflects the approximate percentage of each fatty acid in this oil, composed mostly of C12:0, C14:0, C18:1, C8:0, and C10:0, in this order (see Introduction). Thus, this article differs from previous literature by proposing the use of transesterification (specifically, alcoholysis) starting with only three components - vegetable oil (containing short-chain fatty acids), alcohol, and lipase - to produce odor-active esters with no need for subsequent purification processes. In literature, alcoholysis reactions are mostly used for biodiesel production (Xia et al., 2024), while conventional esterification reactions are commonly employed for aroma production (Sá et al., 2017).

Table 2
Profile of volatile compounds produced after the lipase-catalyzed transesterification reaction of licuri oil and grain alcohol (this reaction took place at 70°C in the presence of 1 % lipase and 50 % grain alcohol).

Peak	Retention Index	Compound	CAS	Percentage of area in volatiles (%)
1	1197	Ethyl octanoate	000106–32–1	5.99
2	1396	Ethyl decanoate	000110–38–3	7.89
3	1596	Ethyl dodecanoate	000106–33–2	44.99
4	1796	Ethyl tetradecanoate	000124–06–1	15.87
5	1995	Ethyl hexadecanoate	000628–97–7	7.12
6	2178	Ethyl oleate	000111–62–6	18.14

In sensory terms, the odor of this biotransformed oil presented a tropical, fruity, and fatty odor reminiscent of pineapple and coconut. Such attributes are mainly due to ethyl octanoate, which is known to have a waxy, fatty, aldehydic, coconut, creamy, and dairy-like aroma; ethyl decanoate, which has a fruity odor reminiscent of grape, an oily, brandy-like odor; and ethyl dodecanoate, that has a waxy, soapy and floral with a creamy, dairy and fruity nuance. These three esters impact the aroma compounds in pineapple, coconut, and other tropical fruits, such as mango and passion fruit (Burdock, 2006).

After confirming that the reaction could yield desirable odor-active esters, a study was designed to identify the ideal reaction parameters to maximize the formation of the esters associated with tropical aroma, as described next. It is important to emphasize that this study did not seek to convert licuri oil completely into aromatic ethyl esters.

3.2. The effects of the main reaction parameters on esters formation during the biotransformation of licuri oil

The strategy to maximize the formation of the esters associated with tropical aroma in the biotransformed included an initial trial to evaluate the effect of lipase load, the volumetric percentage of grain alcohol, and temperature on the amount (g/L) of ester formation. Subsequently, a new set of trials would be conducted with significant variables in a redefined narrower range. Such a strategy has already been employed to optimize ester production (Kumar and Deswal, 2022) and lipase-catalyzed reactions (Shahedi et al., 2021). In the search for references for the present discussion, we did not find articles that report the production of aroma esters by alcoholysis from licuri oil or other oils with short-chain fatty acids to compare results. This fact reinforces the novelty of the process studied, as well as the importance of knowing the effects of each reaction parameter on esters formation during the biotransformation of licuri oil.

The results from the first set of experiments may be visualized in Table 3. At first glance, it is possible to observe that trial 13 (5 % lipase, 34.8 % grain alcohol, 65,2 % licuri oil, and 53.2°C) yielded the highest production of shorter esters (i.e., from C8 and C10 fatty acids). In comparison, longer esters (i.e., from C12:0, C14:0, C16:0, and C18:1 fatty acids) were favored by higher lipase load, alcohol percentage, and temperature (trial 4). At central points (trials 15–17) yielded intermediate values and a slight variation among the repetitions, indicating

Table 3
Matrix of the experimental design of the first CCDR with the results of ethyl esters production (in g/L).

Trial	Lipase (%, m/v)	Grain alcohol (% v/v)	Temp. (ºC)	Ethyl octanoate	Ethyl decanoate	Ethyl dodecanoate	Ethyl tetradecanoate	Ethyl hexadecanoate	Ethyl oleate
1	2	19.5	60	1.7	1.0	4.3	1.3	0.5	1.2
2	8	19.5	60	4.8	3.2	17.2	4.9	1.9	3.2
3	2	50	60	4.7	2.5	11.0	3.9	1.5	2.7
4	8	50	60	5.5	3.1	19.6	6.0	2.5	3.6
5	2	19.5	80	1.2	0.7	3.8	1.2	0.6	1.2
6	8	19.5	80	3.1	1.9	10.4	2.9	1.2	2.0
7	2	50	80	2.2	1.3	4.5	1.5	0.6	1.0
8	8	50	80	4	2.2	9.1	2.8	1.1	1.8
9	0	34.8	70	0.3	0.2	1.3	0.4	0.1	0.2
10	10	34.8	70	5.2	3.0	13.4	4.0	1.4	2.2
11	5	9.1	70	2.9	1.6	9.0	3.4	1.3	2.0
12	5	60.4	70	4.4	2.4	14.5	4.4	1.8	2.6
13	5	34.8	53.2	5.7	3.3	16.1	4.6	1.7	2.2
14	5	34.8	86.8	1.5	0.9	3.9	1.1	0.5	0.9
15	5	34.8	70	4.1	2.3	9.3	2.9	1.1	1.7
16	5	34.8	70	4	2.2	8.8	2.6	1.0	1.5
17	5	34.8	70	4	2.2	8.8	2.6	1.0	1.6

good process repeatability.

After statistical analysis from this dataset, a quadratic model could be derived to represent how these three parameters affected the production of ethyl octanoate (used as a model, given its higher volatility and its importance to the odor of the biotransformed oil), considering a 95 % confidence level. The resulting equation, including only the statistically significant regression coefficients ($p<0.05$, see Supplementary Table S2), is:

$$\text{Ethyl octanoate (g/L)} = 3.79 + 1.16\ L - 0.37\ L^2 + 0.59\ A - 0.97\ T, \quad (3)$$

L is the lipase load (%, m/v), A is the grain alcohol percentage in the liquid mixture (%, v/v), and T is the temperature (°C). The equation is in coded form.

The analysis of variance (ANOVA) of this model (Supplementary Table S3) suggested that it could be used for a reasonably reliable prediction of ethyl octanoate production even though the parameter of lack of fit is not satisfied (F calculated for adjustment/pure error of 115.1 was higher than the respective F tabulated value of 19.4). The low pure error could explain this fact due to the very low variations at the central points (trials 15–17). Moreover, the relative errors ([experimental value-predicted value]/predicted value) were usually <12 %, except for ethyl octanoate concentrations lower than 1.7 g/L. The graphical representation of Eq. 2 may be seen in Fig. 1.

By analyzing the contour curves (Fig. 1), it becomes clear that ethyl octanoate production may be maximized by applying lower temperatures (<60°C), higher lipase load (>6 %), and higher volumetric percentage of grain alcohol (>45 %). The results showed that temperatures above 60ºC are beyond the optimum temperature of Lipozyme® 435 for the system studied, leading to thermal deactivation of the enzyme. However, considering the absence of a quadratic effect for temperature and volumetric percentage of grain alcohol (no inflection point achieved in the range tested), a second set of trials was decided to run at redefined narrower ranges, varying the percentage of grain alcohol (50.90–79.10 %) and the temperature of the reaction (36.9–58.1ºC).

A higher amount of biocatalyst aids in rapidly forming the enzyme-substrate complex, increasing conversion rates. However, excessive enzyme quantities can cause accumulation, blocking substrate sites and not contributing to the reaction rate. Therefore, the enzyme amount must be balanced to ensure high conversion efficiency and low cost (Sá et al., 2017). Thus, for economic reasons, lipase load was fixed at 7.0 %, which is not higher since this represents the highest cost of this procedure.

The results obtained for each trial of this second set of experiments can be visualized in Table 4. As observed in the previous experiments (Table 3), a low variation of the results was evidenced at the central point (tests 9–11), indicating the good reproducibility of these results. Moreover, the concentration of all esters was found at trial 3 (55 % of grain alcohol and 55°C).

The statistical analysis of this set of experiments also resulted in a quadratic model describing ethyl octanoate production according to the volumetric percentage of grain alcohol and temperature, considering a 95 % confidence level (Supplementary Table S4). The resulting equation (Eq. 3) and its graphical representation (Fig. 2) are presented below. The analysis of variance for this new model indicated an even better fit for the experimental results (Supplementary Table S5).

$$\text{Ethyl octanoate (g/L)} = 4.79 - 1.13\ A + 0.50\ T - 0.50\ A.T \quad (4)$$

A is the grain alcohol percentage in the liquid mixture (%, v/v), and T is the temperature (°C). The equation is in coded form.

By analyzing the contour curve (Fig. 2), it can be seen that higher temperatures (in the range between 56 and 58.1ºC) and lower volumetric percentages of grain alcohol (50.9–54 %) tend to favor ethyl octanoate formation. This is also close to the ideal ranges observed in the former experiments (Fig. 1). The polar nature of this reagent explains the negative effect of the percentage of grain alcohol in the mixture. This reagent interacts hydrophilically with the water layer on the surface of the lipase, altering its structure and consequently reducing its activity (Sá et al., 2017). It is worth mentioning that when licuri oil conversion instead of ester concentration was used as dependent variable, a similar profile in the responses could be observed and the same optimal point

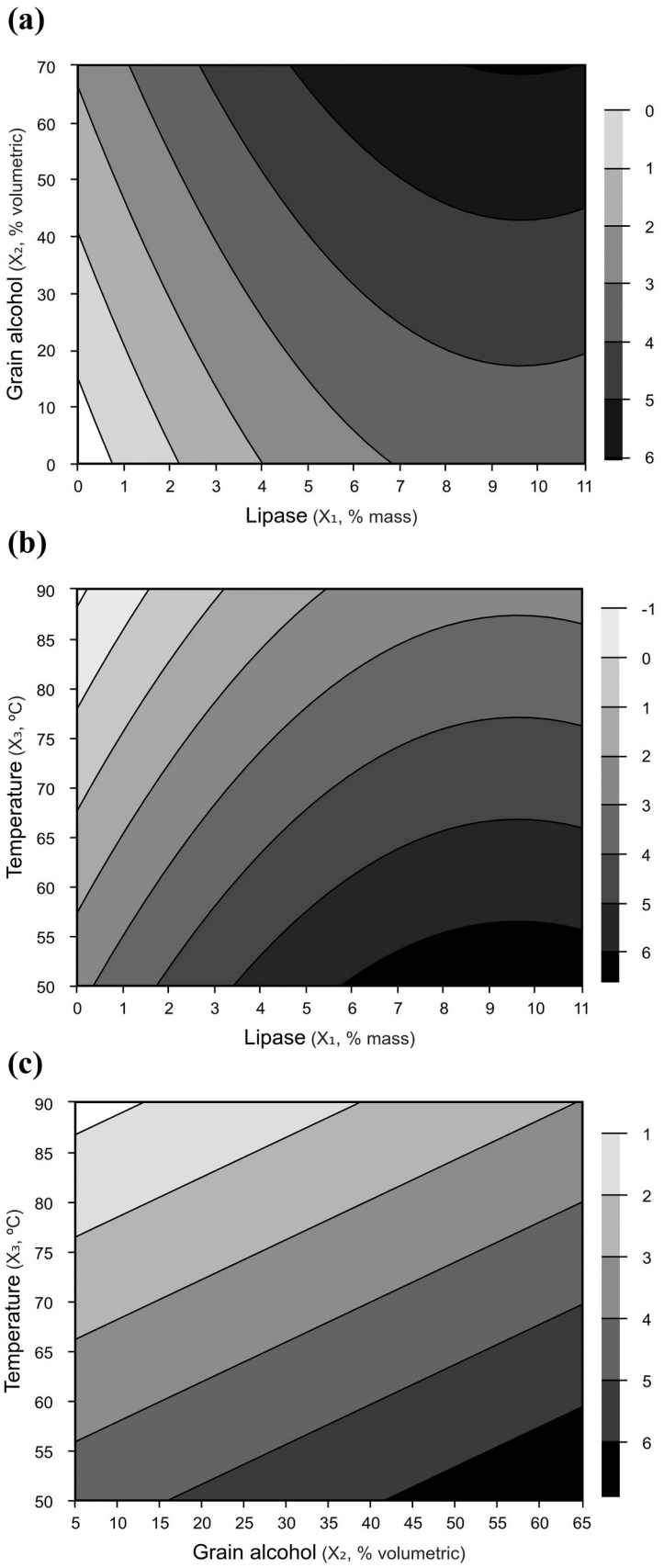

Fig. 1. Contour curves for the production of ethyl octanoate (g/L) after 6 hours of reaction as a function of (a) Lipase (X_1) × Grain alcohol (X_2), (b) Lipase (X_1) × Temperature (X_3), (c) Grain alcohol (X_2) × Temperature (X_3).

Table 4
Results of ester production during esterification reaction for 6 h with 7 % lipase load and varied grain alcohol volumetric percentage and temperatures.

Trial	Grain alcohol (% v/v)	Temperature (°C)	Ethyl octanoate	Ethyl decanoate	Ethyl dodecanoate	Ethyl tetradecanoate	Ethyl hexadecanoate	Ethyl oleate
1	55.0	40.0	4.7	2.4	10.7	3.3	1.3	1.9
2	75.0	40.0	3.3	1.8	8.8	3.2	1.3	2.0
3	55.0	55.0	7	3.9	21.4	6.5	2.5	3.2
4	75.0	55.0	3.6	1.7	9.5	2.8	1.3	1.6
5	50.9	47.5	6.2	3.1	14.8	4.1	1.4	1.8
6	79.1	47.5	3.2	1.6	8.5	2.6	2.5	1.5
7	65.0	36.9	4.3	2.1	9.2	3.1	1.2	1.8
8	65.0	58.1	5.3	2.6	15.2	4.2	1.6	2.6
9	65.0	47.5	4.9	2.4	12.2	3.7	1.4	1.9
10	65.0	47.5	5.1	2.5	13.2	3.9	1.5	2.1
11	65.0	47.5	5.1	2.6	13.5	4.1	1.6	2.2

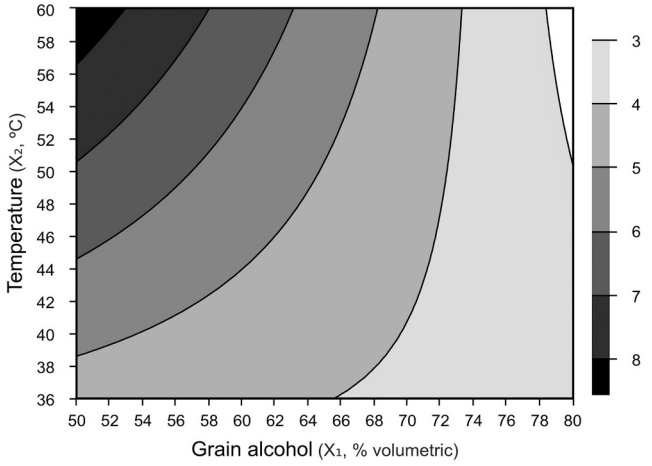

Fig. 2. Contour curve for the production of ethyl octanoate after 6 hours of reaction as a function of Grain alcohol (X_1) × Temperature (X_2).

was identified (data not shown).

A validation experiment was performed at conditions close to the optimal values pointed by both curves (Figs. 1 and 2), i.e., 51 % of grain alcohol, 7.0 % of lipase, and 58°C. The result obtained (8.22 ± 0.62 g/L ethyl octanoate) is less than 2 % higher than the predicted value at these conditions, according to Eq. 3 (8.06 ± 0.34). This validates the model and also reinforces its predictability. This value is also almost four times higher than the ethyl octanoate production at the center points of the first CCDR, representing a significant increase in the production of this odor-active ester.

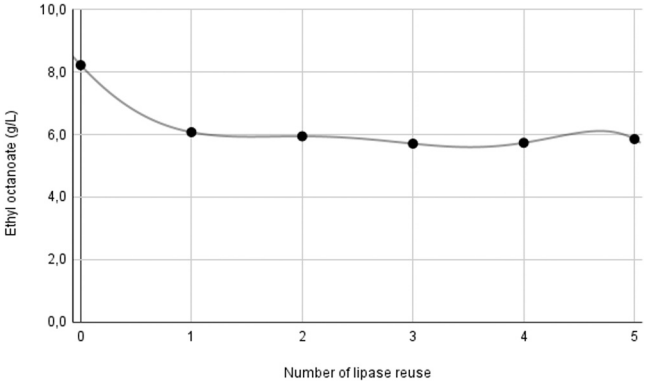

Fig. 3. Residual biotransformation after lipase reuse.

3.3. Enzyme reuse

The data presented in Fig. 3 shows that Lipozyme 435 lost around 26 % of activity (calculated as the % decrease in the production of esters formed by the reaction compared to cycle 0, with ethyl octanoate being used as a reference for the calculation) after the second reuse. After that, the production of esters was kept constant for 4 reuse cycles, using 7.0 % of the enzyme.

The results suggest that the enzyme may also support more than five cycles, decreasing the operational costs for licuri oil biotransformation production. A similar enzyme (Novozym 435) supported 10 reuse cycles in the fish oil transesterification process for biodiesel production, with a loss of 16 % of its activity (Marín-Suárez et al., 2019). For the process of producing geraniol esters using microwaves, Lipozyme 435 was reused 5 times without compromising conversion, continuously decreasing its conversion until the tenth cycle (Venturi et al., 2023). In order to improve the reusability of lipase in our process, other forms of washing can be tested, with other more non-polar solvents, such as hexane, for example, under the hypothesis that non-polar solvents would help to remove the surface layer of oil formed around the enzyme (Hsu et al., 2004). Furthermore, a more significant number of enzymatic recycling should be tested in future experiments.

3.4. Stability of moisturizing formulations

The moisturizing cream remained white, smooth, and uniform throughout the 60-day study. At the same time, the tonic, initially a cloudy oil-in-water emulsion, became more translucent and waterier, indicating complete phase separation and destabilization by the end of the trial at all tested temperatures (5, 25, and 40°C). There was no apparent fungal growth in any sample at any of the temperatures tested. The phase separation tests of the moisturizing creams showed good stability, with no separation between aqueous and oily phases.

Regarding pH, the tonic samples maintained a pH between 4.21 and 4.32 (data not shown) during the study. There was no difference between the pHs of tonics formulated with either 1.0 or 1.5 % biotransformed oil. For the moisturizing cream, the pHs remained between 4.50 and 4.85 during the follow-up period (data not shown), and the formulations with 1.5 % biotransformed oil had a pH value approximately 0.1 unit in comparison to the creams with 1.0 % biotransformed oil. The pH values (between 4.0 and 5.0) follow what is expected for dermo-cosmetic products, aiming to maintain the skin's natural barrier and microflora and provide moisturizing power (Lambers et al., 2006).

Regarding the analysis of volatiles (data not shown), during the first 15 days of storage, ethyl octanoate decreased significantly. Moisturizing creams lost about 70 % when stored at 5°C and about 98 % at 25°C and 40°C, with no difference between creams with 1.0 % or 1.5 % biotransformed oil. Moisturizing tonics showed a 70 % loss at refrigeration and room temperature and an 85 % loss at 40°C, with no difference between the two oil concentrations.

Although the stability of the formulations developed was lower than

expected, these products are a proof of concept indicating that it is possible to formulate cosmetic products (creams and tonics) with biotransformed licuri oil. However, further developments are still required to prolong the shelf-life of these products.

3.5. Antimicrobial effect of the biotransformed licuri oil

It is known that many essential oils present antimicrobial activity (Abers et al., 2021), in a way that these substances can be employed as food ingredients and cosmetic formulations to replace conventional preservatives (Falleh et al., 2020; Guzmán and Lucia, 2021). Individual aroma compounds, including some esters, have also been investigated in this sense (Shaaban et al., 2021). Therefore, this study also evaluated the antimicrobial properties of the biotransformed licuri oil. The target microorganisms were *Staphylococcus hominis*, *S. epidermidis,* and *Corynebacterium xerosis*, model organisms for bacteria responsible for the bad odor of human axillar skin (Troccaz et al., 2015).

The results from the present study indicated that the biotransformed licuri oil had a bactericidal action against *Staphylococcus hominis* (MBC 12.5 μL/mL oil and MIC 6.25 μL/mL oil), *Staphylococcus epidermidis* (MBC 12.5 μL/mL and MIC 6.25 μL/mL) and *Corynebacterium xerosis* (MBC and MIC action with 0.4 μL/mL oil). The analysis of the antibacterial effect of pure licuri oil (prior to the biotransformation process) did not show inhibited the growth of these bacteria at the range tested (10–0.00195 %), suggesting that the antimicrobial effect of the biotransformed licuri oil is due to the esters present.

Active ingredients such as berberine (MIC = 64 μg/mL) (Wojtyczka et al., 2014) had their antimicrobial action tested against *Staphylococcus hominis* ATCC 27844, a non-biofilm-forming bacterium often used as a negative control in antimicrobial studies with more resistant *Staphylococcus* species (Mendoza-Olazarán et al., 2015). Against *Staphylococcus epidermidis* ATCC 12228, antimicrobial activities of violacein were evaluated (MIC = 10 μg/mL and MBC = 20 μg/mL) (Dodou et al., 2017), cinnamaldehyde (MIC = 300 μg/mL and MBC = 600 μg/mL) (Albano et al., 2019), triclosan (MIC = 0.195 μg/mL and MBC = 0.195 μg/mL), hops extract (MIC = 25 μg/mL and MBC > 25 μg/mL), humulone (MIC > 50 μg/mL) (Dumas et al., 2009), antibiotics such as teicoplanin (MIC = 3.1 μg/mL and MBC = 6.25 μg/mL), tetraciclyn (MIC > 8 μg/mL and MBC > 8 μg/mL), and gentamicin (MIC = 0.31 μg/mL and MBC = 0.31 μg/mL) (Selegård et al., 2019) were evaluated in previous studies. *Corynebacterium xerosis* ATCC 373 was evaluated against triclosan (MIC = 3.125 μg/mL and MBC = 3.125 μg/mL), hops extract (MIC = 6.25 μg/mL and MBC = 25 μg/mL), humulone (MIC > 100 μg/mL) (Dumas et al., 2009).

Thus, the biotransformed oil resulting from this study presented a significant antimicrobial effect against the selected bacteria, showing greater potential deodorant power (bacteriostatic and bactericidal) than other natural alternatives previously studied. As expected, the antimicrobial action of biotransformed oil is inferior when compared to drugs used to treat *Staphylococcus* strains in hospital settings.

Based on these results and also in a preliminary formulation assay, a concentration of 1.5 % of biotransformed licuri oil was suggested to impart both a pleasant odor and a significant antimicrobial activity against bacteria responsible for the bad odor of human skin, as described in a Brazilian patent application from our group, which also shows that this process is not exclusive of licuri oil (Moreira et al., 2024). Therefore, this biotransformed licuri oil could be used in cosmetic formulations to impart at least two desirable properties: odor and antimicrobial activity.

4. Conclusion

This study described a process for obtaining an enzyme-catalyzed biotransformed licuri oil composed of ethyl esters, particularly volatile esters presenting tropical fruit notes. The esters from this biotransformed oil also presented a significant antimicrobial activity against bacteria associated with human's bad smell. Therefore, this biotransformed oil, with *in situ*-formed bioactive esters, could be employed as a "natural" ingredient in a cosmetic formulation to improve odor and antimicrobial action. It is worth mentioning that this biotransformed oil could be used without any previous process for recovering and purifying the esters formed since both the unreacted grain alcohol and licuri oil are already employed in cosmetic formulations. This approach can be an alternative to overcome the usually high purification processes of odor-active volatiles, enabling the economic adoption of this and other bioaromas in commercial formulations. Although this study involved only the formulation of a cosmetic product, it seems reasonable to suggest that it could also be used as a food ingredient, impairing similar desirable attributes to this product. Finally, this process is aligned with the most recent demands for sustainability because, apart from the lower energy and material expenses (no need for purification), licuri is a palm tree with an important socioeconomic status since many communities from the Brazilian caatinga and cerrado the depend on the collection of its fruit to live. Thus, the product described in this study can be considered an example of integrating sustainable extractivism and technology in a bio-based economy.

CRediT authorship contribution statement

Juliano Lemos Bicas: Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Gislaine Ricci Leonardi:** Writing – review & editing, Resources, Methodology, Conceptualization. **Rafael Chelala Moreira:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors declare that they have a patent application (BR102024007414–9) related to the results presented in this document.

Data availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jbiotec.2024.06.010.

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