SOURSOP SEED OIL (*Annona muricata L.*): CHARACTERIZATION OF AN EMOLLIENT INGREDIENT FOR COSMETICS

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Abstract

The soursop fruit (*Annona muricata L.*) has edible pulp, and its remains are discarded after processing by the food industry. To mitigate this waste, oil can be extracted from soursop seeds, promoting sustainability. Rich in fatty acids, vegetable oils are ideal for tissue hydration and repair, making them suitable for cosmetics. Emulsions are effective for incorporating soursop seed oil (SSO) into cosmetics due to their enhanced skin absorption and versatility.

This study aimed to characterize the fatty acid profile of SSO, evaluate its cytotoxicity, incorporate it into an emulsion, and assess the preliminary stability of the final product. SSO was analyzed using Fourier transform ion cyclotron resonance mass spectrometry (ESI FT-ICR MS). Cytotoxicity was evaluated with a methyl-thiazolyl-tetrazolium assay on L929 murine fibroblast cells, with SSO solubilized in dimethyl sulfoxide or polysorbate 80. Cell viability was calculated using absorbance averages. An emulsion containing 5% SSO was developed and subjected to preliminary stability testing. Results indicated that SSO contains fatty acids and acetogenins, which possess anti-inflammatory properties that benefit the skin barrier. Cytotoxicity tests showed cell viability at all SSO concentrations. The stable emulsion, made from natural and sustainable raw materials, confirmed SSO's potential as a cosmetic ingredient.

Keywords: Soursop Seed Oil; Sustainability; Fatty Acid; Cytotoxicity; Stability.

Introduction

Soursop (*Annona muricata L.*) is a tropical fruit valued for its edible pulp, widely used in the food industry for the production of frozen pulps, ice creams, juices, and dairy beverages. According to the 2017 Agricultural Census, the national production value of soursop exceeded R$24 million, with more than 7.5 million units of fruit produced. After the pulp is utilized, its peels and seeds are thrown away, adding up to 30 to 40% of the fruit's total weight as waste. It is estimated that, on average, 2 thousand tons of waste from this fruit are generated per year, most of which is discarded in the open air [1,2].

Nowadays, with the growth of sustainable trends, the cosmetic industry seeks to use vegetable oils in its formulations, and one of its sources is the waste from the agri-food industry, such as peels, stems, and seeds. In this context, a mitigating strategy for the disposal of soursop waste involves extracting oil from its seeds, offering a viable and sustainable solution to reduce the environmental impact associated with the production chain of this fruit. By using agricultural

by-products, the cosmetic industry can meet consumer demand for sustainable products while contributing to a circular economy. This production model aims to maximize resource utilization, minimize environmental impact, and promote innovation in material reuse [3].

Natural and sustainable cosmetics have been steadily increasing their market share. According to Fontenelle [4], by this year, this trend will reach a large part of Brazilian consumers, generating competitiveness in the industry. Natural cosmetics are characterized by the incorporation of at least one ingredient derived from a natural substance, not produced by synthesis [5,6].

Used in cosmetology for their emollient function, due to their properties in tissue repair and maintaining the skin's pH, vegetable oils are primarily composed of triglycerides, which, when in contact with the skin, release fatty acids that can benefit the skin's lipid barrier [7]. It should be considered that the method of extracting oil from a plant can influence its chemical composition. When the cold pressing technique is used, it tends to maintain the integrity of vitamins, antioxidants, and essential fatty acids, while methods that use high temperatures or chemical solvents can lead to the degradation of thermolabile compounds and the presence of solvent residues. Therefore, characterizing vegetable oil becomes essential whenever the extraction method is changed [8].

Additionally, to incorporate a new ingredient into a cosmetic formulation, it is crucial to ensure consumer safety. To this end, evaluating the cytotoxic profile can ensure that a new raw material does not cause cellular damage, as the skin is the primary barrier against external agents, and damage to this organ can lead to irritation, sensitization, discomfort, and in more severe cases, systemic effects. A detailed analysis of the cytotoxic profile of vegetable oils helps identify and eliminate any risk of cellular toxicity, ensuring that the final products do not induce adverse responses [9].

For the application of soursop seed oil (SSO) in a cosmetic, one of the most commonly used forms is an emulsion, as it promotes better absorption by the skin and is widely utilized due to

its ability to present itself in different consistencies and its pleasant sensory experience for the consumer. However, since cosmetics can undergo physical changes such as color, odor, and viscosity modification, it is important to understand the product's characteristics and stability during the formulation development. These factors are associated with the product's expiration date and storage conditions. This information can be obtained through a stability study by simulating extreme conditions of temperature, humidity, and light to which the sample will be subjected [10]. The stability study can be used as a predictive tool for instabilities such as phase separation, caking formation, coalescence, and changes in viscosity and pH [11].

In this context, this work aimed to characterize SSO, develop a natural emulsion, and assess the preliminary stability of the final product, focusing on the search for a novel cosmetic excipient.

Materials and Methods

Structure determination

SSO was dissolved in acetonitrile:toluene (1:1). The analysis was run in the positive mode of ESI, with a range of 100/1000 m/z, using Electrospray Ionization Fourier Transform Ion Cyclotron Resonance Mass Spectrometry (ESI FT-ICR MS). All mass spectra were calibrated with sodium trifluoroacetate (NaTFA) with a range of 200-1200 m/z. The software data analysis 4.1 was used to identify the molecular formulas and compared to the databases.

Cell viability

Cell viability was assessed by using the MTT method [12], with some modifications. The murine fibroblasts lineage L929 (ATCC®CCL-1 NCTC) was cultured in *Dulbecco's modified Eagle médium* (DMEM, Sigma-Aldrich) with 10% fetal bovine serum and 1% penicillin/streptomycin. The cells were maintained at 37°C and 5% CO_2 until they reached 80% confluence.

For the viability assessment, fibroblasts were transferred to a 96-well microplate, with a cell density of 5 x 10³ cells/well, and incubated for 24 hours in a humidified incubator at 37ºC with a 5% CO2 atmosphere. Subsequently, the medium was removed and 100 µL of supplemented DMEM medium (10% FBS and 1% antibiotic solution) containing soursop oil at concentrations ranging from 6.25 to 200 µg/mL were added, obtained by serial dilution and in quadruplicate. The soursop oil was previously diluted using dimethyl sulfoxide (DMSO) or polysorbate 80 solution.

As controls, supplemented DMEM medium (negative control), DMEM medium with the solvent [0.1% (v/v) DMSO solution or 0.016% (v/v) polysorbate 80 solution], and 5% (v/v) DMSO solution (positive control) were used. The microplate was incubated for 24 hours at 37ºC with 5% CO_2.

After that period, the culture medium was removed from each well, washed with PBS, and 100 µl of MTT solution (0.5 µg/mL) was added. After 3 hours, the precipitate, formazan, was dissolved in 100 µL of DMSO, and the absorbance was read at 595 nm in a microplate reader. The percentage of cell viability was calculated by comparing the absorbance of treated cells with negative control (100% cell viability). The comparison between the means of the cell viability values in percentage was performed using the ANOVA/DUNNET test. The differences were considered statistically significant at the level of $p < 0.05$.

Preparation of emulsions

The emulsions were prepared according to the methodology of Morais and collaborators [13], using the emulsion phase inversion (EPI) method, in which the aqueous and oily phases were heated in a water bath until they reached an approximate temperature of 70ºC. With similar temperatures, the aqueous phase was incorporated into the oily phase while still being heated, where it remained under manual agitation for five minutes. Then, during the cooling phase, the emulsion was mixed using a mechanical stirrer (FISATON) at a speed of 400 rpm until it reached room temperature.

Preliminary Stability Test

The preliminary stability of the emulsions was evaluated immediately after their manufacture. Centrifugation and thermal stress tests were performed. For the centrifugation test, 5 g of each sample in Falcon tubes were centrifuged under different cycles (1000, 2500, and 3500 rpm) for 15 minutes each. For the thermal stress test, 5 g of samples in Falcon tubes were weighed and subjected to temperatures ranging from 40ºC to 60ºC in a water bath, with a heating ramp of 10ºC every half hour. At each temperature cycle, samples were taken and centrifuged at 2000 rpm for 10 minutes. The formulation selected after these tests was stored at room temperature for 35 days. The organoleptic characteristics and pH were analyzed immediately after preparation (day 1) and on days 7, 14, and 35 [14].

Results

Characterization of SSO

The obtained mass spectrum shows two distinct regions, both with signals of very high resolution, indicating that the proposed molecular formulas are highly accurate. The region shown in the graph with lower m/z ion values corresponds to fatty acids, while the regions with higher m/z ion values correspond to acetogenins. Among the detected fatty acids, the strong intensity of the signals suggests the more abundant presence of palmitic, stearic, hydroxystearic, eicosanoic, hydroxyeicosanoic, dihydroxyeicosanoic, erucic, and hydroxyerucic acids. Among the higher m/z ion values, the acetogenins squamocin, montanacin, annonacinone, and gonionenin stand out. The analysis confirms an oil rich in fatty acids and acetogenins, characteristic of *Annona* species (Table I).

Table I - Suggested compounds in SSO (+)-ESI-FT-ICR MS, 200-700 m/z

NO	m/z	SIGNAL INTENSITY	FORMULA	COMPOUNDS
1	274.27399	77.5	$C_{16}H_{32}O_2$	PALMITIC ACID
2	302.30527	30.4	$C_{18}H_{36}O_2$	STEARIC ACID
3	318.30018	79.2	$C_{18}H_{36}O_3$	HYDROXYSTEARIC ACID
4	330.33654	12,8	$C_{20}H_{40}O_2$	EICOSANOIC ACID
5	346.33149	25.7	$C_{18}H_{36}O_3$	HYDROXYEICOSANOIC ACID
6	362.3264	25.9	$C_{18}H_{36}O_4$	DIHYDROXYEICOSANOIC ACID
7	374.36275	12.5	$C_{22}H_{44}O_3$	HYDROXYERUCIC ACID
8	601.44355	98.2	$C_{35}H_{62}O_6$	SQUAMOCIN
9	615.42282	20.2	$C_{35}H_{60}O_7$	MONTANACIN
10	617.43845	100.0	$C_{35}H_{62}O_7$	ANNONACINONE
11	619.45405	16.5	$C_{35}H_{64}O_7$	ANNONACIN
12	645.46981	32.2	$C_{35}H_{66}O_7$	GONIONENIN

Figure 1. Mass spectra of SSO. **(+)-ESI-FT-ICR MS**, 200-500 m/z.

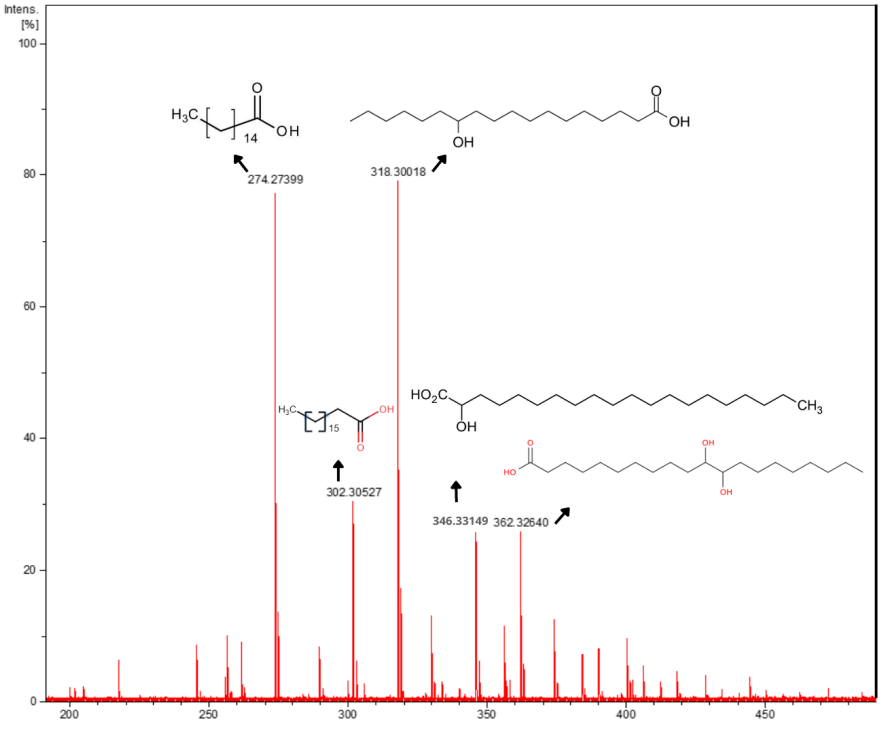
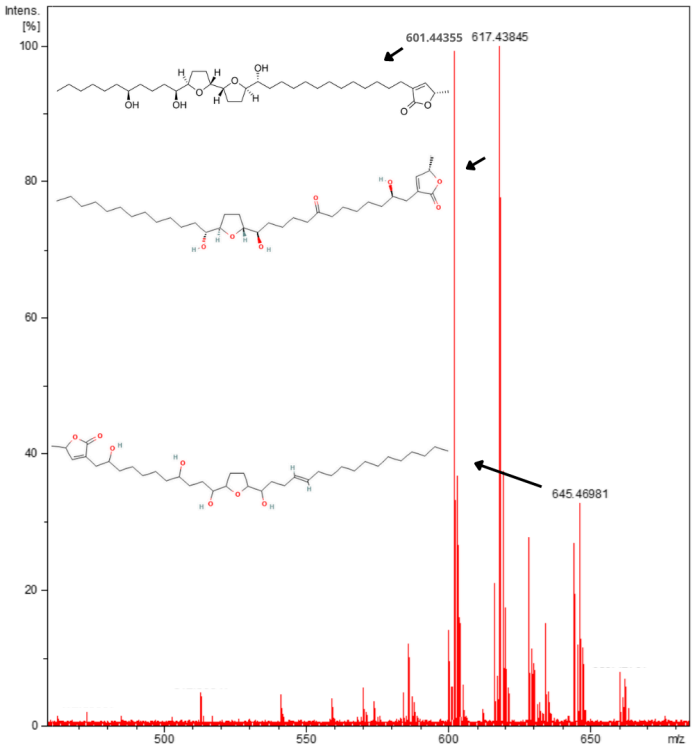


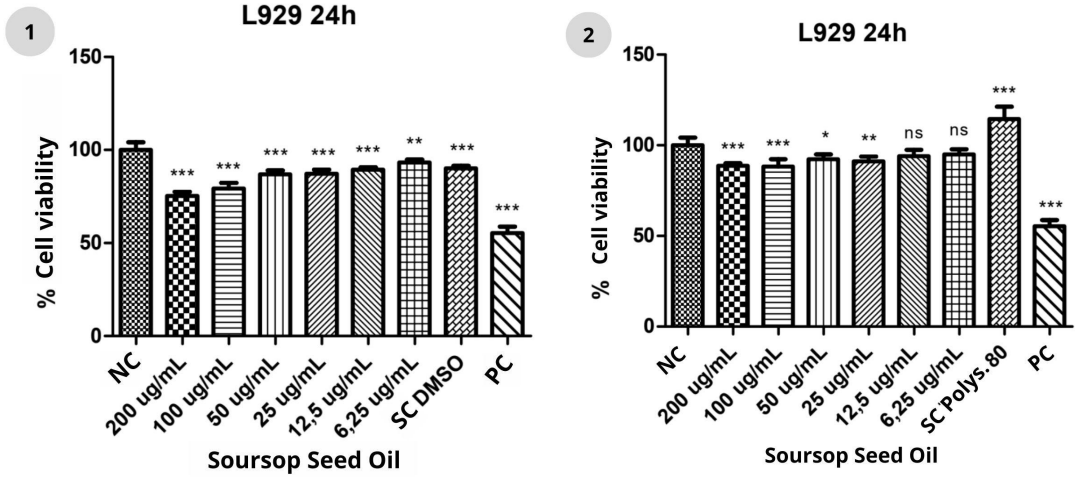
Figure 2. Mass spectra of SSO. **(+)-ESI-FT-ICR MS**, 500-700 m/z.



Cell viability assay

Murine fibroblasts (L929) were used to evaluate the cell viability of SSO. The fibroblasts can be used as a model for testing the cytotoxicity of compounds or products for dermatological or cosmetic formulations [15]. The assay indicated that cell viability was not affected by SSO at the tested concentrations (6.25 to 200 µg/mL) of SSO dissolved in DMSO or polysorbate 80 solution. The cell viability of L929 was greater than 70% at the concentration of 200 µg/mL of SSO. The results are illustrated in figure 3.

Figure 3 - Cytotoxicity assessment by MTT assay in L929 cells following the exposure during 24h of SSO [1: solubilized in DMSO; and 2: solubilized in Polysorbate 80].



The concentration range was 200 to 6.25 µg/mL. Data are presented as means of values ± SD (n = 4). The significance of the results was calculated by one-way ANOVA followed by Dunnet, used as post hoc. Cell growth control corresponds to 100% viability.

Significant values: (*) $p < 0.05$; (**) $p < 0.01$; (***) $p < 0.001$ compared to negative control; ns: no significance; PC: positive control (DMSO 5%); NC: negative control (untreated cells); SC DMSO: DMSO solvent control; SC Polys. 80 (polysorbate 80): Polysorbate 80 solvent control.

Manufacturing of emulsions

Emulsions were developed using SSOl as an emollient excipient. For this purpose, a base formulation with essential components for emulsion formation was taken as a reference, and from there, natural components were chosen to create a sustainable and natural emulsion (Table II).

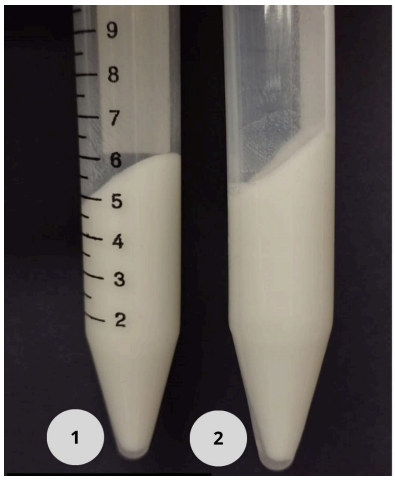
Table II - Emulsion composition

COMPOSITION	CONCENTRATION
Cetearyl Olivate (And) Sorbitan Olivate	10
Cetearyl Alcohol (And) Cetyl Palmitate (And) Sorbitan Palmitate (And) Sorbitan Oleate	2.5
Tocopheryl Acetate	0,5
Annona Muricata Seed Oil	2.5 OR 5 OR 10
Glycerol	5
Caprylhydroxamic Acid (And) Benzyl Alcohol (And) Glycerin	0.5
Aqua	100

The result of the development was a highly moisturizing cream with a pleasant sensory experience and without aggressive active ingredients that could irritate the skin. Therefore, the formulation is ideal for those seeking a deeply hydrating and gentle product, with entirely natural origins and sustainably sourced raw materials.

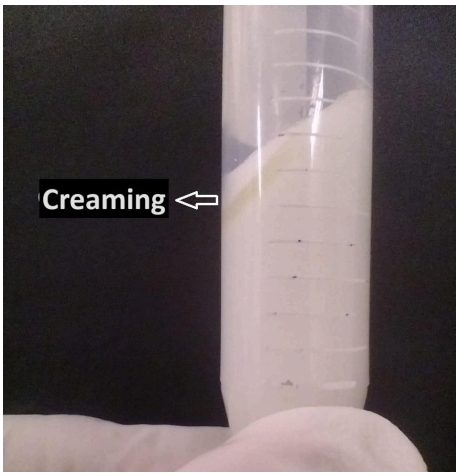
With the developed formulation, emulsions were produced in triplicate to test their stability and determine the best concentration of SSO to be used. The formulations containing 2.5% and 5% SSO remained stable, meaning they did not show phase separation after all cycles of the centrifuge test and the heating ramp test, indicating the suitability of the chosen components for the formulation and the concentrations of oil used.

Figure 4 - Samples containing 5% SSO after 1: centrifuge and 2: thermal stress tests.



Therefore, for the developed formulation, it is necessary that the oil percentage in the formulation is less than 10%, with proven stability in formulations with SSO percentages up to 5%.

Figure 5 - Sample of the formulation with 10% unstable SSO after the last cycle of the thermal stress test.



The chosen formulation for the preliminary stability study was the emulsion containing 5% SSO. It was stored for 35 days at room temperature and did not undergo any changes in color,

odor, or appearance. Considering a confidence interval of 95% and a significance level of $p < 0.05$ as statistically significant, it was found that the pH variation observed over the 35 days was not significant ($p = 0.094$), and the values are shown in Table III. The 5% SSO cream remained within the appropriate range (5-6) for skin application.

Table III - pH values of the 5% SSO cream during storage at room temperature..

DAY	PH*
1	5.66 ± 0.08
7	5.95 ± 0.15
14	5.95 ± 0.16
35	5.86 ± 0.14

*Mean ± standard deviation of 3 batches

Discussion

The evaluation of SSO to validate its incorporation into cosmetic products has been studied by our research group. With the ongoing debate on sustainability and upcycling, there is a need to replace synthetic ingredients with natural alternatives. However, it is necessary to understand and determine the characteristics of a new ingredient, from its processing to its use in a commercial product.

Thus, the results obtained from the lipid profile of SSO confirm its rich composition in fatty acids. Among these compounds, hydroxystearic, hydroxyeicosanoic, dihydroxyeicosanoic, and hydroxyerucic acids stand out. These findings are in line with Kunik et al. [16] and demonstrate a higher intensity of saturated fatty acids. Although present in smaller quantities in the human epidermis, they play an important role in maintaining healthy skin. This type of lipid has shown anti-inflammatory potential in *in vitro* tests [17]. Additionally, in a study by Bomfim et al. [18], SSO was able to reduce by approximately 65.7% the edema caused by phenol-induced

inflammation in mouse ears, which may be justified by the high presence of hydroxyl-substituted fatty acids.

Furthermore, acetogenins were identified as components of SSO. Acetogenins are compounds derived from fatty acids and are characteristic of plants in the Annonaceae family. In recent years, this class of substances has gained prominence in scientific research aimed at analyzing their cytotoxic and antitumor potential. Among the proposed mechanisms of action of acetogenins, the one described by Gupta et al. [19] addresses the energy deprivation of tumor cells through blocking oxidative phosphorylation and consequent reduction in ATP levels.

Regarding cytotoxicity studies for topical use of SSO, assays conducted with raw SSO demonstrated that the oil does not interfere with the cell viability of fibroblasts, with values exceeding 70%. According to the International Organization for Standardization (ISO), samples that reduce cell viability to values below 70% can be considered cytotoxic [20].

Considering the safety confirmation of using OSG on the skin, the characteristics of the application site were analyzed to define the parameters of the emulsion that carries this active ingredient. The skin has ideal pH values ranging from 5 to 6, depending on the region analyzed. This more acidic pH forms what is called the acid mantle, which can influence the bactericidal activities of the skin, essential for the health of this organ. The use of very basic substances can cause dysregulation of the enzymes involved in the natural desquamation process of the epidermis and destruction of the acid mantle, which acts as an antibacterial barrier, thus harming the individual's health. For this reason, the pH of the formulation was defined to be maintained in the pH range (5-6). The final emulsions showed a pH close to 6 [21].

To stabilize the system, a self-emulsifying wax derived from olive lipid, composed of Cetearyl Olivate and Sorbitan Olivate, was used. This non-ionic wax forms oil-in-water emulsions and accepts a wide pH range, from 3 to 12. To aid in the stability of the emulsion and increase viscosity, a co-emulsifier composed of Cetearyl Alcohol, Cetyl Palmitate, Sorbitan Palmitate, and Sorbitan Oleate, also derived from olive, with similar properties to the main emulsifier, was

used. Tocopheryl Acetate has an antioxidant function and was used to protect oily substances in the formulation from oxidation, while glycerol was added to increase hydration sensation and provide a velvety effect on the skin. In order to prevent the growth of microorganisms in the final product, a preservative composed of Caprylhydroxamic Acid, Benzyl Alcohol, and Glycerin was used. Annona Muricata Seed Oil was incorporated into the oily phase and is beneficial for the skin's lipid barrier, as its composition, rich in fatty acids, is similar to that of the skin and provides hydration to the skin barrier. In the study by Souza et al. [22], a cream containing SSO was developed with the aim of replacing synthetic ingredients commonly used as emollients (decyl oleate and liquid paraffin). Formulations prepared with SSO at concentrations of 2.5% and 3.75% showed adequate physical stability, pleasant sensory characteristics, pH suitable for topical application, and stability similar to or better than formulations composed of synthetic emollients. As a contribution of this work to the development of a natural formulation, it is worth noting that the results obtained in our study did not involve the use of synthetic emollients.

Conclusion

The main focus of the research was the analysis of SSO as a new emollient ingredient that can be incorporated into cosmetic formulations. Its sustainable extraction helps utilize natural resources that would otherwise be discarded, thus reducing the environmental impact caused by the agri-food industry. For incorporation into cosmetics, it was crucial to determine its characteristics to ensure safe use and identify its potential benefits for the skin. The characterization of the oil revealed a composition rich in fatty acids and acetogenins, known for their emollient and anti-inflammatory potential. These components, due to their similar structure to the skin's lipid barrier, are beneficial for skin health and contribute to the hydration and maintenance of the lipid barrier. Cytotoxicity assays demonstrated that SSO is safe for topical use, as it did not show cytotoxic effects at the tested concentrations on murine fibroblasts L929.

To incorporate SSO into a cosmetic product, a formulation with natural raw materials was developed. As a result, a highly moisturizing cream with pleasant sensory characteristics and no aggressive ingredients was obtained, ideal for those seeking a gentle, natural, and sustainable product. This formulation underwent preliminary stability testing, subjected to centrifugation and heating ramp tests. The formulation containing 5% SSO remained stable throughout all stages of the tests, indicating good product stability.

Thus, it is concluded that the incorporation of SSO into cosmetic formulations is safe, feasible, and can bring benefits to skin health, while promoting sustainability. Therefore, SSO becomes a viable substitute for traditional synthetic ingredients, aligning with consumer trends towards natural and sustainable products.

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Conflict of Interest Statement

The authors declare no conflict of interests.

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