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Formulation study for the development of a gel/cream produced with Mauritia flexuosa (buriti oil)

Marcos Aurélio Alves de Santana[1], Neusa Barros Dantas Neta[2], Gleiciane de Souza Pereira[3], Mariana Silva Souza[4]

[1,2]Master in Biotechnology and Basic Health Care, UniFacid University Center, Teresina, PI, Brazil, 64052-410
[3]Graduated in Physical Therapy, Christus College of Piauí, Piripiri, PI, Brazil, 64260-000
[4]Graduated in Nursing, Christus College of Piauí, Piripiri, PI, Brazil, 64260-000

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***Abstract*—** *Mauritia flexuosa, known as 'buriti', is an excellent source of bioactive compounds with antioxidant, hypolipidaemic, sun protection, antiplatelet, antithrombotic, hypoglycaemic, antimicrobial and antitumour properties. Considering these properties, it could be used as a therapeutic for conditions that affect the mouth, such as ulcerations and erythema. Among the oral conditions, we can mention oral mucositis, which is characterised by erythema, atrophy and ulceration of the mucous membrane. Thus, this work aimed to develop a phytotherapeutic pharmaceutical formulation for oral application that contains 5% buriti oil as the active ingredient. Five formulations were developed, and one (F5) of the formulations was chosen and subjected to organoleptic and physicochemical analysis (pH, density, and high-performance liquid crhromatography - HPLC), and later to a 3-month stability study in an accelerated climactic chamber. The initially obtained gel/cream was stable according to the tests to which it was submitted. However, after storage for 3 months, it showed a markedly reduced density, indicating the loss of volatile compounds, possibly vitamins A and E. Overall, the gel/cream formulated with buriti oil displays characteristics that make it potentially suitable for the treatment of oral ulcerations such as oral mucositis.*

I. INTRODUCTION

Mauritia flexuosa, known as 'buriti', belongs to the *Arecaceae family* and subfamily *Lepidocarycideae* and is a popular fruit found throughout South America. It is found in the Brazilian Cerrado, most commonly in the states of Pará, Amazonas, Maranhão, Piauí, Bahia, Ceará and Tocantins (Canuto *et al*., 2010). This fruit is an excellent source of bioactive compounds with antioxidant, hypolipemic, sun protection, antiplatelet, antithrombotic, hypoglycaemic, antimicrobial and antitumour properties (Freire *et al*., 2016). Methanolic extracts of various buriti parts show antimicrobial potential against *Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Micrococcus luteus* and *Bacillus cereus* (Koolen *et al*., 2013).

This fruit has macro- and micronutrients of great relevance for the development of new products in the food, therapeutic and pharmaceutical sectors (Freire *et al*., 2016). Considering its properties, it could be used as a therapeutic for ulcerative conditions in the mouth, such as oral mucositis (OM). OM is a common complication of cancer treatment, characterised by erythema, atrophy and ulceration of the mucous membrane of the mouth, leading to ulcer formation (Alhussain *et al*., 2021). It is painful due to exposure of the connective tissue, elevating the adhesiveness of fungi and colonisation of bacteria (such as

Staphylococcus), which exacerbates the pain and risk of infection (Souza & Viana, 2019). Thus, several adverse effects occur, such as intense pain, odynophagia, ulcerations and difficulty eating (Bowen & Wardill, 2017).

Although there are forms of treatment and prevention (oral hygiene, laser therapy and oral cryotherapy) and resources that relieve the symptoms of OM (analgesics and anti-inflammatory drugs, among others), there is still not an effective, specific treatment of OM that completely covers all its manifestations (Lima *et al*., 2021). The use of phytotherapy, along with multi-professional action, could have an indication for use and reduce intercurrences during antineoplastic treatment in individuals with cancer (Souza & Viana, 2019). Therefore, the search for new therapies that promote symptom relief and act to reduce and prevent OM is crucial (Lima *et al*., 2021). In this context, the purpose of this project was to develop an alternative phytotherapeutic pharmaceutical formulation containing buriti oil as a natural, low-cost active ingredient for oral topical use. The physicochemical characteristics of the gel/cream formulation were determined be measuring the pH and density and performing a centrifugation test, and the stability of vitamins A and E, which are present in buriti oil, was evaluated.

II. METHODOLOGY

2.1 Obtaining the raw material

The raw material was obtained from Engetec Engenharia das Essências, a Brazilian supplier of Amazonian buriti oil located in São Paulo, SP. According to the supplier, the vegetable oil is obtained by cold pressing the pulp, without refining, and it is 100% pure. It is non-volatile and has a strong colour and odour.

2.2 Physicochemical tests

A specified procedure (Brasil, 2008) was used to examined the physicochemical properties of the gel/cream. The physicochemical tests adopted for oil characterisation were appearance (viscous liquid), colour (reddish), odour (characteristic), density (0.910 g/mL), acidity index (9.4%), the iodine index (74.36 cg l/1002 g), the peroxide index (3.19 mEq O/kg2), the saponification index (197 mg KOH/kg) and the refractive index (1.46980) (Silva, 2019).

2.3 Chromatographic assay

Chromatography is one of the most versatile techniques for separating mixtures of substances. There is differential migration of substances in a chromatographic system that comprises the mixture to be separated, the mobile phase (gas or liquid) and the stationary phase. HPLC differs from other liquid chromatography techniques because of its ability to reduce the size of particles, allowing more efficient separation (Andrei *et al*., 2011).

The chromatographic profile in the raw material – to identify and quantify its fatty acids – was obtained by performing high-resolution gas chromatography using an HP 7820A gas chromatograph, with a Supelcowax-10 column (30 m × mm2 × 0.2 µm; Supelco). The column temperature was 150ºC, the injector temperature was 250°C and the flame ionisation detector was 260°C. The sample (1 µL) was injected with a 1:20 split ratio. The column temperature was increased up to 250°C at 10ºC/min. The following fatty acids were found in the raw material: palmitic acid (17.69%); oleic acid (74.03%); linoleic acid (2.14%); linolenic acid (1.24%); and stearic acid, gondoic acid and other compounds that were not quantified.

2.4 Location and equipment for bioproduct handling

The gel/cream was formulated in collaboration with companies located in the city of Floriano, PI. The equipment for physicochemical tests – pH, density, centrifugation and chromatography (HPLC and column) (Figure 1) – were duly calibrated and qualified before being used.

Fig.1. Equipment used for the physicochemical tests. A Fisatom model 713 mechanical stirrer; B stainless steel beaker; C Gehaka BG 4000 balance; D glassware; E hotplate; F plastic rod, digital thermometer, spatula and breadboard; G digital pH meter; H model 80-2 B centrifuge; I metal pycnometer; J HPLC; and K column.

2.5 Stability study

The raw materials that made up the formulation (Table 1) are suitable for use when stored properly and used before the expiration date. The stability study was performed by using a Mecalor stability chamber, equipped

with precision temperature and humidity control in accordance with the standards and conditions of the Brazilian Health Regulatory Agency (Anvisa). The climatic chamber was previously calibrated and its maintenance programme was up to date. The study was conducted at 40°C ± 2°C 75% ± 5% relative humidity (RH); these conditions allow for expected and tolerated variations due to climatic chamber openings. This study is designed to accelerate the chemical degradation and/or physical changes of a pharmaceutical product under forced storage conditions (Brasil, 2019a).

Table 1. Pharmaceutical excipients used in the development and characterisation of the orabase pharmaceutical formulation produced with buriti oil (Mauritia flexuosa) and their respective applications and registration numbers.

EXCIPIENT	CAS NO.	APPLICATIONS[1]
Aspartame	22839-47-0	Sweetening agent
Mint essence	-	Flavouring
Cetyl Alcohol	36653-82-4	Coating, emulsifying and hardening agent
BHT	128-37-0	Antioxidant
CMC	9004-32-4	Stabilising, suspending, viscosity-increasing and water-absorbing agent
EDTA	6381-92-6	Chelating agent
Glycerine	56-81-5	Antimicrobial preservative; co-solvent; emollient; humectant; plasticiser; solvent; sweetening and tonicity agent
Xanthan gum	11138-66-2	Gelling, stabilising, suspending, sustained-release and viscosity-enhancing agent
PEG 4000	25322-68-3	Ointment base; plasticiser; solvent; suppository base; tablet and capsule lubricant
PEG 400		
Nipagin	99-76-3	Antimicrobial preservative
Nipazol	94-13-3	
Solid petroleum jelly	8009-03-8	Emollient; ointment base
Ollivem 1000®	85116-80-9/92202-01-2	Emulsifier

[1]According to Rower et al. (2009). Abbreviations: BHT, butylated hydroxytoluene; CMC, carboxymethyl cellulose; EDTA, ethylenediaminetetraacetic acid; PEG, polyethylene glycol.

2.6 Bioproduct development

During the development of the gel/cream, five formulations were produced in an attempt to stabilise the product. The raw materials and concentrations used in each formulation are shown as percentages in Table 2.

Table 2. Raw materials and their respective concentrations used in the five formulations (F1–F5).

RAW MATERIAL	F1	F2	F3	F4	F5
EDTA	0.05 %	0.05 %	0.05 %	0.05 %	0.05%
Glycerine	5.0%	5.0%	5.0%	5.0%	5.0%
Xanthan gum	0.2%	0.2%	0.2%	0.2%	0.2%
CMC	0.3%	0.3%	0.3%	0.3%	0.3%
Distilled water	37.9 %	36.9 %	32.4 %	35.3 %	35.3%
PEG 4000	8.0%	8.0%	8.0%	8.0%	8.0%
PEG 400	20%	20%	20%	20%	20%
Solid Vaseline	20%	20%	20%	20%	20%
Cetyl Alcohol	3.0%	3.0%	3.0%	3.0%	3.0%
BHT	0.05 %	0.05 %	0.05 %	0.05 %	0.05%
Phenonip®	0.5%	-	0.5%	-	-
Mint essence	-	-	2.0%	1.5%	1.5%
Simulgel®	-	0.5%	-	-	-
Cetiol V®	-	-	3.0%	-	-
Ollivem ®1000	-	-	-	6.0%	1.0%
Aspartame®	-	0.5%	0.5%	0.5%	0.5%
Buriti Oil	5%	5%	5%	5%	5%
Optiphen®	-	0.5%	-	-	-
Nipagin	-	-	-	0.05 %	0.05%
Nipazol	-	-	-	0.05 %	0.05%
Total (%)	100%	100%	100%	100%	100%

Abbreviations: -, not included in the formulation; BHT, butylated hydroxytoluene; CMC, carboxymethyl cellulose;

EDTA, ethylenediaminetetraacetic acid; PEG, polyethylene glycol.

Except for formulation F5, after solubilisation the raw materials that composed the aqueous phase were poured into the raw materials that composed the oily phase that had also been solubilised; both phases were at 60°C. At the end, the active ingredient and the other adjuvants were added.

To prepare the final formulation (F5), distilled water was measured in a plastic beaker and then added to a stainless-steel beaker. Ethylenediaminetetraacetic acid (EDTA) and glycerine were then weighed and added separately to the beaker; the mixture was stirred by hand until completely solubilised, and then heated to 80°C. Next, nipagin was added and the mixture was stirred until completely solubilised. Carboxymethyl cellulose (CMC) was sprayed and stirred until completely solubilised; subsequently, the xanthan gum added and the mixture was stirred, always maintaining the temperature at 80°C, thus creating the aqueous phase (phase 1).

In a separate glass beaker, the raw materials of the oil phase were weighed: PEG 4000, PEG 400, solid Vaseline, cetyl alcohol, butylated hydroxytoluene (BHT) and nipazol. They were then dissolved 80°C and under constant stirring to produce the oily phase (phase 02).

Immediately after heating, with both phases at approximately 60°C, the oily phase was slowly poured over the aqueous phase under agitation in the Fisatom Mod. 713 mechanical stirrers at 200 rpm. The stirring was maintained until room temperature was reached. The Olivem® 1000 was partly heated to complete dissolution and added to the beaker under stirring. Aspartame® was also partly dissolved in water (approximately 5 mL) and added to the beaker under stirring. In the final step at 40°C, buriti oil was added and stirred constantly. Finally, the mint essence was added and the mixture was stirred for approximately 20 min (Brasil, 2019b).

After the preparation of the product, quality control analyses were performed to evaluate the physical and chemical stability of the gel/cream obtained. The centrifugation, density in a metal pycnometer and pH tests were performed; the last two were performed in triplicate to evaluate the reproducibility of the results. All procedures were carried out as specified in Farmacopéia Brasileira, 6th edition (Brasil, 2019b) and the Cosmetic Products Stability Guide (Brasil, 2004).

The product was kept at room temperature (25 ± 2°C) for 48 h and then analysed. Part of the product was distributed in a petri dish for evaluation of the organoleptic characteristics colour, taste, odour and the presence or absence of lumps (clumps of particles). These parameters were evaluated through smell, sight, taste and touch. Subsequently, the gel/cream was subjected to the centrifugation test. Equal amounts of the product were separated in three test tubes, placed in a centrifuge (Centribio model 80-2 B) and centrifuged at 3,000 rpm for 30 min (Brasil, 2004). The relative density was determined by using a metal pycnometer. The pH was determined at room temperature (25.0 ± 2.0°C) by using a Mettler Toledo benchtop digital pH meter that had been calibrated with pH 4.0–7.0 buffer solutions. The sample was also subjected to analysis for identification of the bioactive compounds of vitamin A (retinol) and vitamin E (tocopherol) (Monograph, 2017; Food Chemicals Codex, 2020). Additional details of the analyses are presented in section 2.7.

2.7 Physicochemical assay of the bioproduct

2.7.1 Density

After weighing the empty metal pycnometer and taring the balance, the sample was inserted into the metal pycnometer and then weighed. The formula below was used to determine the density. The weight of the empty pycnometer was 148.3779 g/mL and the weight difference of the pycnometer with water and the empty pycnometer was 25.0475 g/mL.

$$\left(d_{20}^{20}\right) = \frac{\text{pycnometer weight with sample} - \text{empty pycnometer}}{\text{Weight difference of the pycnometer with water and the empty pycnometer}}$$

2.7.2 pH

The pH of the sample was measured in a Mettler Toledo benchtop digital pH meter by inserting the electrode directly into the sample. The electrode was removed from the resting solution (water), washed and placed inside the product. After allowing the reading to stabilise, the measurement was recorded.

2.7.3 Identification of vitamins A and E

For vitamin A identification, 6 µg of the sample was weighed in a glass beaker and dissolved in 1 mL of chloroform. Next, 10 mL of antimony trichloride working solution was added to the solution. For vitamin E identification, 50 µg of the sample was dissolved in 10 mL of absolute alcohol. Two millilitres of nitric acid was added under stirring and the solution was heated.

The chromatographic analysis was performed with fresh solutions following the principles of the European Pharmacopoeia 9th edition (European Directorate for the Quality of Medicines, 2017) with some adaptations. One millilitre of the sample solution was pipetted into 10 mL of dichloromethane and dissolved. The stationary phase was octadecylsilyl silica gel for chromatography reagent (5 µm). The mobile phase was water reagente and methanol reagent (5:95 v/v). An ultraviolet (UV) spectrophotometer was used to detect vitamins A and E, with 10 µL of the sample and standard solution injected.

After completing the initial analysis of the formulation, nine aluminium tubes (60 g capacity) were filled with the product. After being identified with an adhesive label, the samples were submitted to the accelerated stability study. Storage in the accelerated climactic chamber lasted for 3 months at 40 ± 2°C and 75% ± 5% RH (Brasil, 2019b). The sample was analysed again to determine its stability.

2.8 Statistical analysis

The sample results were analysed by means of descriptive statistics (obtained from MATLAB) and organised in a Microsoft Excel spreadsheet. The statistical variables used are: mean, variance, standard deviation, minimum and maximum. Student's t-test was performed to evaluate the stability and pH changes after 3 months of storage. A p value < 0.05 was considered to indicate a significant difference.

III. RESULTS

The gel/cream obtained had the typical characteristics of a viscous gel, had no lumps and had a yellow colour, from the buriti oil. Overall, it was a uniform product, had a pleasant texture, was easily spread and had a characteristic mint odour/flavour that lasted even after 3 months of incubation in the accelerated climactic chamber (Figure 2). There was no phase separation in the initial sample subjected to centrifugation, making the formulation suitable for the stability study in the accelerated climactic chamber.

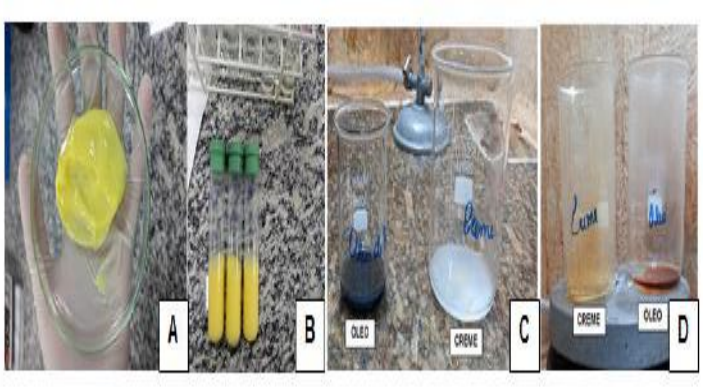

Fig.2. A Appearance of the gel/cream obtained with 5% buriti oil; B the appearance after the initial centrifugation (before stability testing); C colourimetric identification of vitamin A; and D colourimetric identification of vitamin E.

The pH and density analyses of the gel/cream were performed in triplicate. The values before and after the stability study in the accelerated climatic chamber are presented in Table 3.

Table 3. The pH and density of the formulated gel/cream before and after the stability study in an accelerated climatic chamber for 3 months (n = 3 for each time point, presented separately).

DESCRIPTIVE STATISTICAL ANALYSIS

Parameters	Analysis 1	Analysis 2	Analysis 3	Initial average
pH	6.16	5.99	5.97	6.04
Density (g/mL)	2.5221	2.5721	2.5555	2.5499

Parameters	Analysis 4	Analysis 5	Analysis 6	Final average	Standard deviation	Variance
pH	6.46	6.39	6.06	6.30	0.21	0.04
Density (g/mL)	0.9703	0.9703	0.9735	0.9714	1.12	1.25

In the colourimetric identification of vitamin A before and after the stability study, the desirable confirmation of retinol (vitamin A) in the sample would be the immediate appearance of a transient blue colour. In the analysed sample it was not possible to clearly observe the colour transition because of the whitish colouration from the solution extracted for analysis (Figure 2). However, using high-performance liquid chromatography (HPLC), there

was a peak in the retention time of about 4 min in the initial sample, indicating the presence of the vitamin A in the product. The peak was no long present in the sample after 3 months of storage in the accelerated climactic chamber (Figure 3). Before and after the stability study, vitamin E was successfully identified based on the colourimetric assay: a bright red to orange colour developed upon heating, confirming the presence of tocopherol (vitamin E) in the product.

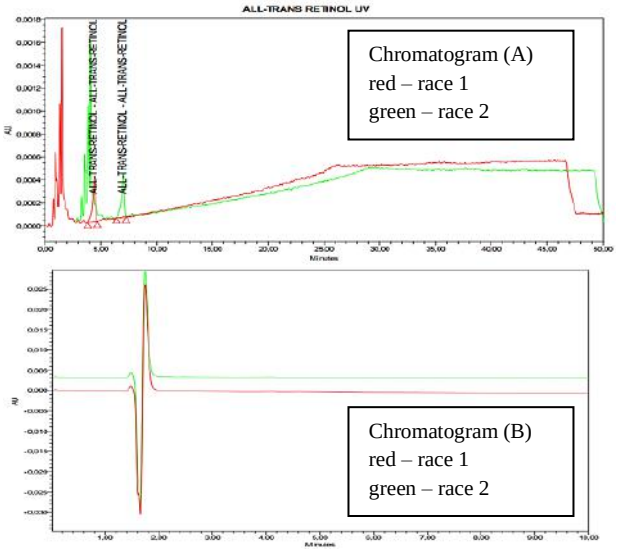

Fig.3 UV-HPLC Chromatogram (A) obtained before the accelerated stability study identifying the presence of the vitamin A precursor all-trans retinol in the bioproduct sample. Chromatogram (B) obtained after an accelerated stability study identifying the absence of the vitamin A precursor all-trans retinol in a sample of the bioproduct.

Abbreviations: UV, ultraviolet; HPLC, high-performance liquid chromatography.

All the results for the product analysed prior to long-term storage were satisfactory. There was no difference in the pH of the product before and after the stability study ($p > 0.12$). However, after the accelerated stability study, the density had dropped significantly ($p < 0.12$), which indicates a loss of volatile components. This reduction is probably related to a loss of vitamin A, because the associated chromatographic peaks no longer appeared after storage for 3 months.

IV. DISCUSSION

A gel-type semisolid pharmaceutical form is composed of one or more active ingredients containing a gelling agent. The cream consists of an emulsion, formed by a lipophilic phase and a hydrophilic phase (Brasil, 2019b). The product produced in this study had the characteristics of both a gel and a cream, and these characteristics were maintained before and after the stability study.

Centrifugation analysis is a primary test performed before a stability study to anticipate possible instability. Phase separation could occur in semi-solid forms (Brasil, 2004). In this test, the product did not show any sign of instability; hence, the product was submitted to the stability study.

The density of a liquid or semi-solid form can indicate the incorporation of air or the loss of volatile ingredients (Brasil, 2004). The gel/cream formulated with buriti oil had an initial average density of 2.5499 g/mL. After 3 months of storage in the accelerated climactic chamber, the density had dropped markedly to 0.9714 g/mL; this difference was significant ($p < 0.12$). This change indicates that there was a loss of volatile ingredients in the formulation.

The pH represents the acidity or alkalinity of a given solution, measured from 1 (acidic medium) to 14 (alkaline medium), with 7 being considered a neutral pH (Brasil, 2004). The normal pH of saliva in the mouth is around 7 (RizqI et al., 2013). The pH of the product was close to the neutral pH of saliva, which indicates a good indication for oral use. The pH of the formulated gel/cream did not change after 3 months of storage in the accelerated climactic chamber.

Vitamin A deserves special attention for its importance in combating oxidative stress and its potential chemoprotective effect (Matos *et al.*, 2014). The colourimetric identification of vitamin A was not clear, probably due to interference from the colour of the sample. Specifically, after extraction with chloroform, the sample solution had a whitish colour, which could have caused interference, making the analysis impossible, because it is visual. When the test is performed using buriti oil, the blue colour is clearly visible, confirming the presence of vitamin A in the oil used in the product.

The sample was then subjected to a more effective analysis via HPLC, obtaining satisfactory results in the initial analysis, with a vitamin A identified at 4 min at 325 nm. The time differs from that specified by the European Pharmacopoeia 9th edition (Monograph, 2017) due to the column used, which was of a different size (Zorbax Eclipse C18 150 m × 4 mm). Because it was longer in length, the run time varied, but did not exceed the acceptable limits for variations in chromatographic parameters (column diameter ± 25%) (Brasil, 2019b). However, in the chromatogram obtained after the stability study, no peak was observed. The vitamin A had probably degraded, which is consistent with the considerably reduced density of the formulation after long-term storage.

Alpha-tocopherol is the main component of the vitamin E breakdown group. It is a powerful antioxidant and the main fat-soluble vitamin responsible for protecting cell membranes from peroxidation (Lima *et al*., 2014). The colorimetric identification of vitamin E was fully satisfactory and as expected: both before and after the stability study, the product contained vitamin E.

Vitamins A and E are relatively stable but can exhibit significant losses due to thermal degradation during storage and because they are easily oxidised in the presence of oxygen (Prado *et al*., 2011). Thus, it is suggested that further studies be conducted to better ascertain the stability of these compounds and to verify the antimicrobial and antifungal properties of the new formulation produced with buriti oil.

V. CONCLUSION

Based on the results obtained, the orabase gel/cream formulated with buriti oil showed initial stability and the expected physicochemical properties. That is, there was no visible instability observed in the product such as phase separation and it was possible to detect the presence of vitamins A and E, bioactive compounds with important antioxidant activity. After 90 days of storage in the accelerated climactic chamber, although the formulation did not present phase separation, there was a marked drop in the density compared with the initial analysis. This reduction indicated the loss of volatile compounds, a fact confirmed later by the absence of the vitamin A chromatographic peak. The absence of vitamins does not disqualify the product as a good candidate for the treatment of OM, because it maintained its fatty acid composition, including linoleic (omega or 6n-6) and linolenic acid (omega 3 or n-3) acids, which are essential for normal cellular functions of the skin. Additional studies should be carried out to improve the stability of especially vitamin A and to explore the antimicrobial and antifungal properties of the bioproduct developed in this research. Other improvements could also be made, such as changing the flavour. The mint essence could be replaced by any other flavour that is pleasant to the target audience.

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