Received: 29 March 2024 | Revised: 16 May 2024 | Accepted: 28 May 2024
DOI: 10.48309/JMPCR.2024.450357.1163
Journal of Medicinal and Pharmaceutical Chemistry Research
SAMI

FULL PAPER

Elucidation profile analysis syzygium cumini extract to be developed as oral anti-mucositis gel

Susi Sukmasari[a] |Mohammad Nasrin Abdul Rahman[b,*] |Abd Almonem Doolaanea[c] |Mohd Hafiz Arzmi[d] |Nur Zakirah Mezan[b] |Azyyati Mohammad Muzafar Shah[b] |Puteri Izz Khayrin Maghzan[e]

[a]*Department of Paediatric Dentistry and Dental Public Health, Kulliyyah of Dentistry, International Islamic University Malaysia, Kuantan Campus, 25200 Kuantan, Pahang*

[b]*Department of Pharmaceutical Technology, Faculty of Pharmacy, University College MAIWP International, 68100 Kuala Lumpur, Malaysia*

[c]*Ph.D. Senior R&D Chemist Sabrena Experience 1500 Dragon Street Suite 160 Dallas, Tx 75207*

[d]*Department of Fundamental Dental and Medical Sciences, Kulliyyah of Dentistry, International Islamic University Malaysia, Kuantan Campus, 25200 Kuantan, Pahang*

[e]*Department of Biotechnology, Kulliyyah of Science, International Islamic University Malaysia, Kuantan Campus, 25200 Kuantan, Pahang*

***Corresponding Author:**
Mohammad Nasrin Abdul Rahman
Email: nasrin@ucmi.edu.my
Tel.: +60102615881

Syzygium cumini is a traditional medicinal plant that has been used to treat various ailments. This study is conducted to characterise the extract contents, rheological, release, and texture profile of *Syzygium cumini* gel to be developed as anti-mucositis gel for dental applications. To determine the phytochemical content, Supercritical Fluid Extraction, and Soxhlet extractions were conducted. Whereas rheological characterisation, release, and texture profiles of five different gels were formulated using SC leaves extracted using sequential cold percolation (toluene, petroleum ether, acetyl acetate, acetone, and water extract). The rheological, release and texture profiles of the gels were then measured using rheometer, incubator shaker, and texture analyser, respectively. It was found that SC leaves extracted using Soxhlet contains the highest total phenolic and catechin content, while epicatechin content was highest in the extract of Supercritical Fluid Extraction with carbon dioxide as solvent at 150 bar. Regarding the gels, water extract gel had the best rheological profile. Although water extract had low permeability coefficient based on the release profile test, there was statistically significance difference in term of permeation rate flux from other gels (P<0.05). Phytochemical content and other related data were successfully documented to help in elucidating the best dental gel to be developed as antimucositis gel.

KEYWORDS

Supercritical fluid extraction; antimucositis; dental; gel; *Rheology*; *Soxhlet*; catechin; epicatechin.

Introduction

Syzygium cumini (SC) is a common herb used by old folks in previous decades for the remedy of various ailments including fever and as agents for wounds management [1]. SC is also called *Eugenia cumini* (Linn.), *Syzygium jambolana* DC., and *Eugenia Jamboolana* Lam. It belonging to Myrtaceae family and is traditionally used in Southeast Asia as well as Brazil to treat diabetes [1,2]. Topical treatments, such as gels, creams, and ointments, were extensively utilized. To create successful topical medicine, it is necessary to optimize many aspects such as the physical appearance, rheological properties, release characteristics, pH level, potential for skin irritation, texture, and spreadability. These

factors are crucial for ensuring that the medication functions as an efficient drug delivery agent [3].

Oral mucositis (OM) is one of the common side effects from radiotherapy treatment for cancers of head and neck. Inflammation is characterized as an unpleasant and painful condition that affects sleep, nutrition, and mood quality. Depending on the patient, the side effects may be divided into three categories: mild, moderate, and severe. It is known that chemotherapeutic therapy affects the oral microbiota, causing bacteremia and septicemia in individuals, particularly those suffering from cancer and neutropenia (low neutrophil count) [4]. Among the most found microbiota in the head and neck of cancer patients during radiation treatment include *Candida albicans*, *Candida kefyr*, *Candida glabrata*, *Candida krusei*, and *Candida tropicalis*. Several anaerobic species were also associated with ulcerative OM such as, *Fusobacterium nucleatum*, *Parvimonasmicra*, *C. glabrata, Treponema denticola*, and *C. kefyr*. The presence of *Porphyromonas gingivalis*is is a key indicator of OM [5,6]. Previously, anaerobic bacteria, such as *F. nucleatum*, *P. gingivalis*, and *Prevotella intermedia*, which are associated with both periodontal disease and periodontal abscesses, emerge on the surface of the buccal cavity after 14 days of chemotherapy, resulting in the loss of equilibrium in the oral microbiome [7]. Furthermore, a complex epithelial structure was used to illustrate the significant consequences of dysbiotic shifts, specifically those related to mucositis, on the decline of the oral mucosa. It was observed that the presence of mucositis-depleted *Streptococcus salivarius* was well-tolerated as a commensal, while the mucositis-enriched *F. nucleatum* exhibited pro-inflammatory and proapoptotic properties [8].

Gel is a substance composed of two components, where there are crosslinks between liquids and polymers in a three-dimensional network. They are three-dimensional networks that incorporate medicinal, cosmetic, or other agents, with sizes normally ranging between 1 nm to 1 mm [9]. This network forms an endless and hard structural framework that can be immobilized and yet flexible [10]. Pharmaceutical product manufacturing typically involves the documentation of physicochemical properties, such as consistency, pH, drug uniformity, release profile homogeneity, and texture analysis test. Prior research has indicated that the viscosity of typical herbal or medicinal gels commonly falls between the range of 4700-4800 cP. In addition, the spreading diameter in the spreadability test was seen to be between 38-55 mm after one minute [11]. The rate at which compounds are released from a topical gel is affected by various factors, including physiological factors (such as the specific location on the body, hydration level, temperature, condition of the skin, and age of the skin) and drug-related factors (such as the size of the molecules, chemical properties of the drug, partition coefficient, and thermodynamic activity of the drug within the gel) [12].

Franz Cell test can either finite or infinite dosing test where both depend on the amount of substance in the dosage wafer. In the infinite dosing, the dose of the active compound/gel applied is large, thus their depletion caused by any external factors such as evaporation is negligible. Thus, the dose available as permeant is considered infinite. On the other side, only limited amount of compound/gel is applied at the dosage wafer for finite dosing setting. This is to imitate *in vivo* diffusion behaviour [13]. Texture profiles analysis test was conducted using human senses in scientific studies in the past. However, there is increasing innovations in analytical instruments that can calculate the textural characterisation of pharmaceutical products such as gels in the recent decades. The data are highly reliable because they are independent from sensory and subjective variations by humans [14]. Texture profile analysis

measures various textural profiles, such as hardness, springiness adhesiveness, gumminess, cohesiveness, resilience, and chewiness [15]. Today, texture profile analyser is successfully used in scientific studies to compare the quantifiable data of hardness, cohesiveness, and adhesiveness of various pharmaceutical products [16].

There is limited study have been done previously that explained thoroughly on the profile analysis of SC to be developed as anti-mucositis gel. Hence, this study aimed to characterise the phytochemical contents which is catechin and epicatechin based on different extraction setting using supercritical fluid extraction methods, the rheological, release, and texture profile of SC leaves extract gel to be developed as anti-mucositis gel. It is expected that the present study would provide a better understanding of the properties and medical benefits of SC. More importantly, the valuable data presented in this paper would serve as a guideline in planning future inspections for preliminary clinical purposes and developing novel pharmaceuticals formulated using active constituents from SC that improves the overall treatment of OM.

Experimental

Chemicals

The chemicals utilized in the extraction process involve ethanol, hexane, petroleum ether, toluene, ethyl acetate, acetone, and methanol. These chemicals were of analytical quality and also were obtained from R&M Chemicals located in Essex, United Kingdom. Carbopol 940 from Acros Organics (Geel, Belgium) was used to create the gels. The chemicals propylene glycol, methyl paraben, propyl paraben, and triethanolamine were obtained from Sigma Aldrich, a company based in Missouri, United States.

Syzygium cumini leaves sources

The extraction process involves the use of leaves samples harvested from Southeast Asia (Kedah Malaysia and Sukorejo, Wonosobo (Central Java, Indonesia). Upon leaves collection, they were washed under running tap water to remove the debris and dirt adhered to the leaves surface. Later, the leaves were subjected to oven-drying at a temperature of 50 °C (Memmert, Germany) for 3 days until it reached a state of crispness and dryness.

To produce the powdered form, the dried sample was crushed and filtered through a sieve with a 40-mesh opening. The leaves were subsequently pulverized into a fine powder, and the mass of the dry powder was measured. Before the studies, the powdered plant was kept in a dry environment and kept in an airtight dark container to prevent moisture absorption. This sample was then extracted in 3 ways, which are Supercritical Fluid Extraction (SFE), Soxhlet apparatus, and Sequential Cold Percolation.

Extraction process

Supercritical fluid extraction

The dried *Syzygium cumini* leaves as in Figure 1 were grounded to form a powder-like texture before extraction process. In SFE, ethanol and carbon dioxide were used as solvents for the extraction using a lab scale plant manufactured by DEVEN. SFE were set up to different pressure which is 150 bar, 250 bar, and 350 bar with 50℃ constant temperature. It is expected that phytochemical content and antioxidant capacity of the leaves to differ according to different pressure and temperature. For the part that uses ethanol solvent and carbon dioxide, 150 g of the sample was weighed, and 30 g of ethanol 20% w/v was added to the SFE for extraction. The sample was placed in the filter bag and was soaked in ethanol solvent. The extraction was run until the sample was completely dried as in Figure 2. Weight before and after of the sample was recorded to calculate the yield percentage.

FIGURE 1 The dried Syzygium Cumini leaves

FIGURE 2 Extract collected from the supercritical fluid extraction process

Soxhlet extraction

The SC leaves were also extracted using Soxhlet extraction method as shown in Figure 3. The finely ground leaves of SC were placed in a thimble chamber of the Soxhlet apparatus in this method. Hexane, ethanol, and petroleum ether were used as extraction solvents. The three solvents were heated in separate bottom flasks before vaporizing into the sample thimble, condensing in the condenser, and dripping back. When the liquid content reaches the siphonarm, it is emptied into the bottom flask, and the process is repeated. Following

the extraction of each different solvent using Soxhlet, the extract is then passed through the rotary evaporator process. A rotary evaporator is a quick and efficient way to remove solvent from a flask. After that, the collected solvents were subsequently dried to complete evaporation using a rotary evaporator (IKA 3V) until complete dryness. A rotary evaporator removes solvent by using vacuum to reduce pressure within the flask, rotating the sample to increase its effective surface area, and heating the solution. The higher the boiling point, the lower the pressure, and when it reaches a low temperature, it will become gas/vapour. The extract was evaporated until it formed a solid or thin film which is crude extract and the crude extract obtained from the round bottom flask was stored at -20 °C prior to further investigation.

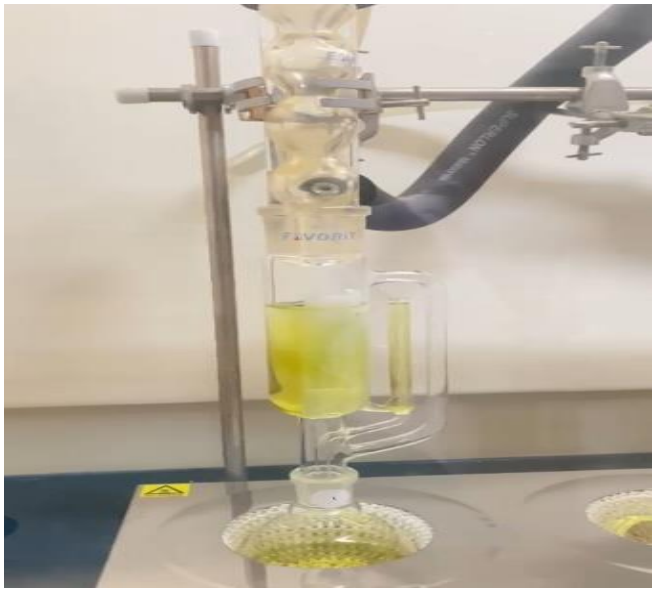

FIGURE 3 Soxhlet extraction process

Sequential cold percolation

The SC leaves were extracted by a sequential cold percolation process. The solvents were employed in a sequential manner, first with petroleum ether, followed by toluene, ethyl acetate, acetone, and finally water. Initially, the desiccated leaf powder was immersed in petroleum ether with a concentration of 10% w/v, which is equivalent to 25 g of powder in 250 mL of petroleum ether, contained in a conical flask. The conical flasks were agitated at a speed of 120 rpm per minute at a temperature of 27 °C using an incubator shaker. After 24 hours, the solvents were subjected to filtration using Whatmann no. 1 filter paper and vacuum filtration to separate the powdered leaves from the solvents. The filtrate underwent centrifugation at a speed of 5000 rpm per minute for 10 minutes at 27 ºC to entirely separate the supernatant from the finely dried leaves powder. The liquid portion was extracted by pipetting, while the solid remnants remained at the bottom of the centrifuge tube. The residual and desiccated leaf powder was extracted utilizing the subsequent solvent (toluene), and the identical technique will be replicated. Subsequently, ethyl acetate will be introduced, followed by acetone, and finally water. The solvents were collected and subsequently dried to dryness using a rotary evaporator. The crude extract obtained from the round bottom flask as in Figure 4 was allowed to dry completely under the fume hood for a further 2 days to remove any leftover solvents. During this procedure, the extracts will be shielded with aluminium foil to keep out from exposure to

light. The raw extract was collected and stored at a temperature of -20 ºC until it is ready for further examination.

Content analysis of SC

Percentage yield

By comparing the weights of the dried leaves with the crude extract generated, percentage yield (% w/w) for sample extracted using SFE was calculated. Three duplicates of the extraction were carried out, and the findings were expressed as mean were documented.

Determination of total phenolic content

Total phenolic content of the sample extracted from both SFE and Soxhlet Extraction methods were quantified using Folin-Ciocalteu reagent. Folin-Ciocalteu reagent was diluted at concentration of 20% w/v in water, while extract samples of 1 mg/mL concentration were prepared for each extract. 100 µL of the diluted Folin-Ciocalteu reagent was pipetted into the single cuvette. 20 µL of the extract sample was added and the mixture was incubated for 5 minutes. Next, 100 µL of 40 % w/v sodium carbonate in water was added into the sample mixture and further incubated for 2 hours at room temperature. Cuvette was covered with aluminium foil to protect the sample mixture from exposure to light to prevent degradation. Total phenolic content was quantified using Folin-Ciocalteu reagent in single cuvette as explained by Ahmed *et al.* Standard curve of Gallic acid was prepared to quantify the total phenolic content of all the extracts. Results were expressed as mean ± SD (n=3) and the values recorded were in mg of Gallic acid equivalent per gram of dried leaves weight (mg GAE/g DW).

Catechin and epicatechin content using LC-MS

The quantity of polyphenols such as catechin and epicatechin were also tested on both samples extracted from SFE and Soxhlet Extraction using Liquid Chromatography-mass Spectrometry (LC-MS). Standard calibration curves with six concentration points were used to evaluate linearity, and each concentration level was measured in triplicate. By dividing the chromatographic peak area of the analyte by the corresponding peak area of the internal standard (1 g/mL), calibration curves were generated. Each calibration line's slope, intercept, and correlation coefficient were calculated using a linear regression analysis. A CLEAN-UP extraction column with C18 (500 mg/3 mL) for solid phase extraction (SPE) were purchased from UCT (Bristol, USA). The column was wetted with methanol and then conditioned with deionized water.

FIGURE 4 The crude extract obtained after drying using rotary evaporator

Characterization of gel incorporated with SC leaves extract

Rheological characterization

Rheological characterization was performed to document the rheological profile of each gel (3% w/w carpool gel) incorporated with SC leaves extracts (3% w/w) produced using sequential cold percolation method, specifically using solvents of petroleum ether, toluene, ethyl acetate, acetone, and water extract. The rheological profiles were measured using Haake MARS Rheometer (Thermo Scientific, Massachusetts, United States) controlled by Haake Rheo-Win 3.61.0000 software. The spindle is of type parallel plate (PP35 Ti) 35 mm diameter. The instrument was set to run at 25±0.05 °C [17]. Initially, the viscosities of the gels were measured at 3 different shear rates which was 30 s^{-1}, 60 s^{-1}, and 120 s^{-1} where setting of controlled rate measurement were used for least 6 seconds. The maximum shear stress to produce shear rate of 120 s^{-1} were also measured by translating the graph for analysis. The linear viscoelasticity range (LVR) was also measured using the job of stress sweep with range of shear stress from 1 τ to 100 τ. The G', G", Tan δ, values were derived from the graph output directly, while difference of G' and G", shear stress 10 where tan δ, the point of G'-G" crossing point, and the rheological modelling using Herschel Bulkley model were determined from the graph analysis.

Release profile characterization

Release profiles test was conducted using gels incorporated with sequential cold percolation SC leaves extract, by employing the infinite dosing Franz diffusion cell apparatus. The Franz diffusion cell system (Hanson Research, Chatsworth, USA) has a capacity of 7 mL receptor cell, and 1.8 cm^2 total diffusion area. The receptor solution used was phosphate buffered saline (PBS) with 7.4 pH [18]. The system temperature was maintained at 37±0.5 °C to mimic the body temperature using circulated water jacket connected to water bath [19]. The membrane used was cellulose acetate membrane with size of 25 mm diameter, and 0.45 µm pore size and 110 µm thickness purchased from PolyScience (Illinois, USA). Prior to experiment, the cellulose acetate membrane was soaked for 30 min in the receptor solution (PBS) at temperature of 37±0.5 °C to hydrate and swell the pores of the membrane [20].

Tweezers were used to mount the cellulose acetate membrane on receptor cells. PBS were filled in the receptor cells with meniscus forming at the surface, to make sure that the solutions touched the cellulose acetate upon running the experiment. Proper care was taken not to produce any bubbles because it will affect the release profile results. Each of the Franz Cell were stirred using cylindrical PTFE magnetic bar (12 x 6 mm) with pivot ring at 300 rpm. This speed was just nice not to produce vortex as it should be prevented so that the static fluid layer at the surface of the receptor solution was not interrupted [21]. Infinite dosing was used with the application of 400 mg of the gel at the dosage wafer which is equivalent to 222.22 mg/cm^2. The system was run for 6 h, and 0.5 mL samples were taken at intervals of 0.5 h, 1 h, 2 h, 4 h, and 6 h with replacement of another new 0.5 mL fresh PBS.

The release profile from Franz Diffusion test was measured by quantifying the total phenolic content of the receptor solution (phosphate buffer) in each time interval. The test technique employed was the Folin-Ciocalteau reagent test [22]. In summary, 50 µL of Folin-Ciocalteau reagent, diluted with water at a ratio of 1:4 (equal to 20% v/v), was put to each well in a 96-well plate. Subsequently, 10 µL of each of the 11 receptor solutions were added and incubated for 5 minutes. Subsequently, 50 µL of a sodium carbonate solution with a concentration of 40% w/v was introduced and incubated for a further 2 hours

at a temperature of 37 °C. The absorbance was measured at a wavelength of 725 nm using a microplate reader called TECAN Infinite 200 PRO, located in Mannedorf, Switzerland. The reader was operated by Tecan icontrol software version 1.6.19.2. A calibration curve was constructed with standard solutions containing Gallic acid. The measurements were conducted three times for each sample, and the outcomes were reported as the equivalent amount of Gallic acid in µg/mL [23].

Texture profile analysis

Texture profile analysis of SC gel incorporated with sequential cold percolation SC leaves extract was performed using Brookfield CT3 Texture Analyzer (Middleboro, USA) as in Figure 5 with setting of TPA mode. The probe used was plastic material of length 3.5 cm x 1.3 cm. Fresh bovine mucosa was used and hydrated with PBS. The trigger force applied on each gel was 50 g, with deformation of 1.5 mm and speed of 0.5 mm/s. About 5 g of gel was attached to the mobile arm of the probe, and the mobile arm was moves slowly towards the bovine mucosa which was attached using double sided at the immobile arm. Five replicates' readings were taken, and the results were expressed as mean ± SD.

Statistical analysis

The data underwent analysed using one-way ANOVA (one-way analysis of variance), followed by Tukey's test for multiple comparisons, utilizing SPSS version 26. The statistical significance of the presented data (mean values provided) was assessed by the p-value, where the data is regarded significantly different if the p-value is less than 0.05.

FIGURE 5 CT3 Texture analyzer used for texture profile analysis

Results and discussion

TABLE 1 Percentage yield of SC leaves extracted using SFE

Solvent	Percentage yield (%)
Ethanol + CO_2 150 bar 50°C	1.25% w/w
Ethanol + CO_2 250 bar 50°C	1.55% w/w
Ethanol + CO_2 350 bar 50°C	1.94% w/w
Carbon dioxide 150 bar 50°C	0.84% w/w
Carbon dioxide 250 bar 50°C	0.62% w/w
Carbon dioxide 350 bar 50°C	0.67% w/w

Based on Table 1, the percentage yield was the highest for ethanol with carbon dioxide solvent at 350 bar, followed by 250 bar and 150 bar. Carbon dioxide was found to have the lowest percentage yield. Ethanol solvent is a universal solvent due to the presence of both polar and non-polar group. This make it easier to dissolve polar and non-polar molecules and it is proven can produce more yield. Other than the polarity of solvent, high pressure can affect the percentage of yield.

Total phenolic content tabulated in Table 2 revealed that for SC leaves extracted using SFE, the method with ethanol and carbon dioxide as solvent at 150 bar was the highest followed by carbon dioxide alone, at 150 bar. The sample extracted using carbon dioxide alone as solvent at 250 bar was the lowest. In light of these findings, it can be concluded that the ethanol extract had a considerable effect on the release of the majority of secondary metabolites from leaves. This might be because polar solvents like aqueous ethanol are frequently used to extract phenolic chemicals in larger concentrations. The polyphenolic concentration of the extract may vary greatly depending on the polarity of the extracting solvents. Since ethanol is a more polar organic solvent than other polar solvents. The majority of the polyphenolics considered in this study are probably polar molecules. Previous findings have emphasized the crucial function that phenolic compounds play in scavenging free radicals. Phenolic antioxidants are by-products of secondary metabolism in plants, and they have significant antioxidant activity as a result of their chemical composition, redox characteristics, and ability to chelate transitional metals. As a result, the total phenolic and flavonoid concentrations of plant/herb extracts are frequently used to explain their antioxidant properties.

SC leaves extracted using Soxhlet method with ethanol as the solvent revealed the highest total phenolic content, followed by hexane, and petroleum ether. This means, extracting using Petroleum ether is not preferable because it has less ability to extract a significant amount of phenolic contents.

TABLE 2 Total phenolic content of SC leaves extract

Extraction Method	SAMPLE NAME	AVERAGE
SFE	Carbon dioxide 150 bar	14.21 Mg GAE/g
	Carbon dioxide 250 bar	9.39 Mg GAE/g
	Carbon dioxide 350 bar	12.48 Mg GAE/g
	Ethanol + CO_2 150 bar	14.89 Mg GAE/g
	Ethanol + CO_2 250 bar	12.78 Mg GAE/g
	Ethanol + CO_2 350 bar	11.32 Mg GAE/g
Soxhlet	Ethanol	56.39 Mg GAE/g
	Hexane	11.95 Mg GAE/g
	Petroleum Ether	8.10 Mg GAE/g

TABLE 3 Catechin and epicatechin content in SC leaves extract

No.	Sample ID	Catechin (µg/g)	Epicatechin (µg/g)
SFE	Carbon dioxide 150 bar	4.5864	785.955
	Carbon dioxide 250 bar	Undetectable	Undetectable
	Carbon dioxide 350 bar	Undetectable	
	Ethanol + CO_2 150 bar	Undetectable	
	Ethanol + CO_2 250 bar	Undetectable	
	Ethanol + CO_2 350 bar	Undetectable	
Soxhlet	Ethanol	5.63	
	Hexane	0.47	
	Petroleum Ether	Undetectable	

One of the previous studies suggests that Epicatechin significantly inhibited radiation-induced apoptosis in keratinocytes. Epicatechin significantly inhibited radiation-induced apoptosis, change of MMP, and intracellular ROS generation in HaCaT cells [24]. Epicatechin treatment markedly attenuated the expression of p-JNK, p-38, and cleaved caspase-3 after irradiation in the HaCaT. Polyphenols such as catechin and epicatechin can be determined using Liquid Chromatography-mass Spectrometry (LCMS) by extracting polyphenols from the sample matrix using a suitable solvent. The result of LC-MS analysis of catechin and epicatechin content in the extracts of SC leaves were consigned in Table 3.

For sample extracted using SFE, the data showed the presence of catechin 4.5864 (µg/g) and epicatechin 785.9546 (µg/g) when extracted using carbon dioxide alone as solvent at 150 bar. The rest of the sample solvent did not show any presence of any flavanols. For sample extracted using Soxhlet method, the data shows that catechin is highly detected in ethanol solvent and lesser in the hexane solvent whereas catechin is undetectable in petroleum ether solvent. For the epicatechin, all three extraction solvents do not show any epicatechin content.

One of the previous studies documented that total phenolic content (TPC) of SC is 79.89 mg of Gallic acid per gram of SC seed kernel (SCSKP), a total flavonoid content (TFC) of 7.29 mg of catechin equivalent per gram of SCSKP, as well as catechin and Gallic acid contents of 0.61 mg/g and 35.9 mg/g of SCSKP. These differences may be expected due to the different methods of extraction and plant sources as also different solvents used to

extract the plant in which they are using Ultrasound-Assisted Extraction (UAE) and used water as the solvents [25]. However, these finding shows that SC plants have the best content of antioxidant as well as a high content of TPC.

TABLE 4 Rheological characterization of different types of SC leaves extract gel

Type of gel	Apparent viscosity at shear rate of			Maximum shear stress (Pa) needed to produce shear rates of 120 s^{-1}	Linear viscoelasticity range		
	30 s^{-1}	60 s^{-1}	120 s^{-1}		G'	G"	Difference of G' and G"
Plain carbopol	56.89±0.76^{a}	35.52±0.08^{a}	25.1 ± 0.03^{a}	3011 ±7.09^{a}	1122.27±9.64^{a}	155.74±3.18^{a}	966.53±6.46^{a}
Pet Ether	34.72±0.68^{b}	21.01±0.17^{b}	14.20±0.05^{b}	1701±2.08^{b}	814.72±24.56^{bc}	109.46±9.23^{b}	705.26±15.33^{bc}
Toluene	34.42±0.02^{b}	21.34±0.03^{c}	13.68±0.02^{c}	1640±3.61^{c}	760.51±19.15^{b}	97.11±8.49^{bc}	663.4±10.66^{b}
Ethyl acetate	33.14±0.02^{c}	20.73±0.03^{d}	13.47±0.01^{d}	1617±1.0^{d}	773.46 ±26.06^{b}	107.18±9.97^{b}	666.28±16.09^{b}
Acetone	31.41±0.04^{d}	19.67±0.01^{e}	12.70±0.01^{e}	111.52±6.48^{b}	1525±1.53^{e}	840.79±35.25^{c}	729.27±28.77^{c}
Water	47.42±0.40^{e}	26.28±0.06^{f}	15.89±0.07^{f}	1902±3.21^{f}	977.39±16.64^{d}	85.75±4.42^{c}	891.64±12.22^{d}

Note: *(a, b, c, d, and e) showed significant differences; G' indicating it is the gel that most likely to behave the most elastic compared to others and G'' indicates the loss modulus which illustrates the gels viscous behaviour measured from its linear viscoelasticity range.

TABLE 5 Rheological modelling of gels incorporating different types of SC leaves extract.

Type of gel	Herschel Bulkley			
	r	τ0 (Pas)	k(Pa sn)	N
Plain carbopol	0.9998	470.4	290	0.4606
Pet Ether	1.000	276.7	166.6	0.4564
Toluene	1.000	248.5	143.3	0.4558
Ethyl Acetate	1.000	302.7	184.2	0.4559
Acetone	1.000	259.8	141.3	0.4530

Note: r: correlation; τ_0: yield stress (Pa); k(Pa sn): the consistency index; and n: flowability index

TABLE 6 Franz diffusion cell (release profile) results

Type of gels	Permeation rate flux (µg/cm²/h)	Permeability coefficient (x10^{-2})
Petroleum Ether	212.41 ± 44.51^{ab}	3.70 ± 0.77^{b}
Toluene	139.79 ± 4.20^{c}	3.20 ± 0.10^{bc}
Ethyl Acetate	230.47 ± 9.55^{a}	6.34 ± 0.26^{a}
Acetone	122.61± 4.71^{c}	2.21 ± 0.08^{cd}
Water	171.8 ± 15.98^{bc}	1.69 ± 0.16^{d}

TABLE 7 Texture analysis of different types of SC leaves extract gel

Type of gel	Hardness (g)	Cohesive	Springiness (mm)	Adhesive (Mj)
Plain Carbopol	194.80 ±19.78^{a}	0.84 ±0.07^{a}	1.16 ± 0.15^{ab}	1.36 ± 0.17^{a}
Pet Ether	180.20 ± 28.87^{a}	0.85 ±0.06^{a}	1.1 ± 0.07^{ab}	1.04 ± 0.15^{ab}
Toluene	162.40 ± 15.53^{ab}	0.90±0.06^{a}	1.18 ± 0.16^{a}	1.02 ± 0.19^{ab}
Ethyl Acetate	153.40 ± 8.56^{ab}	0.86 ±0.05^{a}	1.10 ± 0.1^{ab}	1.04 ± 0.11^{ab}
Acetone	162.40 ±20.23^{ab}	0.80 ± 0.08^{a}	1.14 ± 0.05^{ab}	0.78 ± 0.19^{b}
Water	116.60±4.72^{b}	0.76 ± 0.08^{a}	0.86 ± 0.09^{b}	0.88 ± 0.31^{ab}

Table 4 illustrated rheological characterization of SC dental gel incorporated with different types of SC leaves extracts (produced from sequential cold percolation extraction method). It was found that all the carbopol gels incorporated with SC leaves extract of different solvents, behaves as pseudoplastic gels where the viscosity decreases with increases shear rates of 30 s^{-1}, 60 s^{-1}, and 120 s^{-1}. The viscosity decreases with the incorporation of any SC leaves extract compared to plain carbopol. At shear rate of 30 s^{-1}, viscosity for acetone SC leaves extract gel was found to decrease the most, followed by ethyl acetate, toluene, pet ether, and water SC leaves extract. While at shear rate of 120 s^{-1}, the ranking of gels from least to highest viscosity was as follows: acetone, ethyl acetate, toluene, petroleum ether, and water SC leaves extract. This means that water extract gel behaves as the most viscous gel even at the environment where shear rate is the highest compared to acetone extract gel. Looking at the maximum shear stress needed to produce shear rates of 120 s^{-1}, it was found that water SC leaves extract required the highest shear stress compared to other solvents (petroleum ether, toluene, ethyl acetate, acetone, and water). Comparing with plain carbopol, it was found that plain carbopol required the higher shear stress to produce shear rate of 120 s^{-1} compared to all solvents of SC leaves extract. This means the SC incorporation did reduce the viscosity and makes the gel to develop rate of change of shear easier. The higher the shear stress required to produce the shear rate of 120 s^{-1} is better since oral movement is full of movements and shear. If the gel easily produces shear rate with low shear stress, that means the gel will tend to change behaviour easily (decrease in viscosity) which is not the intended characteristic. A good gel is the one that can resist changes in viscosity in wide range of shear stress. From the viscoelasticity test, it was found that all gels had linear viscoelasticity range (LVR). Having LVR means the gel had a range of shear stress that the gel will remain as viscoelastic gel until the crossing point of G' and G" (which is a good characteristic). G' which indicates the storage modulus illustrates the gel's ability to possess elastic properties.

The higher the value of G' within linear viscoelasticity region, the better the gel is because it will be more elastic and tend to come to original viscoelastic gel when stretched (shear stress is applied). According to Table 4, it was found that all the gels incorporated with all types of SC leaves extract experienced reduction in the value of G' compared to plain carbopol. This means plain carbopol has higher elasticity properties compared to the SC leaves extract gel. The water extract gel had the highest G' value (significantly different) compared to the other SC leaves extract gel. However, no significant difference was found between petroleum ether and acetone SC leaves extract gel, and between petroleum ether, toluene, and ethyl acetate SC leaves extract gel. This means the water SC leaves extract was the most superior in G' value, indicating it is the gel that most likely to behave the most elastic compared to others. G" indicates the loss modulus which illustrates the gels viscous behaviour measured from its linear viscoelasticity range. The lower the G" value means the gel is lesser viscous. However, another parameter that need to be defined was the difference between G' and G" where the larger the difference means the better the gel is, since the distance for both G' and G" to meet up and cross over increases, so they had lesser tendency to crossover compared to those that has smaller distance between G' and G". The crossover of G' and G" indicates the breakdown of the gels network, means they will not behave as viscoelastic gel anymore after G' and G" crossed. Based on Table 4, it was found that plane carbopol gel has the highest G'- G" differences, followed by water SC leaves extract gel. Petroleum ether however was found not having significant difference with toluene, ethyl acetate, and acetone SC leaves extract. Water SC leaves extract gel might have

the least G" value compared to other gel, but this also illustrates that it has larger differences of G' and G" which is acceptable as the intended characteristic for mucositis in mucous membrane application.

Tan δ explains how viscous the gel is, where the lesser the value of tan δ, the viscous the gel is. According to Table 4, it was illustrated that all the tan δ values were not significantly difference between the plain carbopol and the SC leaves extract gels of petroleum ether, toluene, ethyl acetate, and acetone ($p > 0.05$), except for water extract ($p < 0.05$). The value of tan δ for water SC leaves extract gel was 0.09, lower compared to all the other extract gels, including plain carbopol. This means the viscosity of the water SC leaves extract gel in term of tan δ is higher compared to others, which is a good characteristic of a mucositis dental gel. Regarding the value of shear stress where tan $\delta = 1$, this information illustrated the location of where the gel will turn into a liquid state (tan $\delta = 1$). The higher shear stress in order for the tan δ achieve value of 1, is the better because it means the gel will need a lot of shear stress to convert the gel behaviour to be liquid. Plane carbopol gel was found to demand the highest shear stress compared to other gels, followed by water SC leaves extract gel. Acetone SC leaves extract gel was found to demand the lowest shear stress value to achieve tan δ value of 1, which means the gel will easily become liquid even with less shear stress was applied compared to other gels. Petroleum ether, toluene, ethyl acetate, and acetone SC leaves extract gel all possess shear stress of < 1000 Pa to achieve tan δ of 1, which means they do not have a good criterion as water SC leaves extract gel that has value of shear stress > 1000 Pa. Another criterion to be considered is the location where crossing point of G' and G" happens. Plane carbopol and water SC leaves extract gel was found to happen at the highest shear rate which was at 1,857 Pa and 1216 Pa, respectively, meaning the crossing point of G' and G" happens further away from all other SC leaves extract gel. Besides, the exact value of G' and G" was highest for plane carbopol gel as well as water SC leaves extract gel. This means water extracts possess high crossing point due to high G' value, thus illustrating that they are a good viscoelastic gel with high G' (storage modulus). Petroleum ether, toluene, ethyl acetate, and water SC leaves extract gel was found to had lower crossing point of G' and G", meaning their G' is not high enough to store the modulus in order to possess a good elastic gel.

Table 5 indicates the rheological modelling of all the SC leaves extract gels. All the gels exhibit Herschel Bulkley modelling, as described in Equation (1):

$$\tau = \tau_0 + K(y)^n \quad (1)$$

Where, τ is shear stress (Pa), τ_0 is yield stress (Pa), K is consistency factor, y is shear rate (s^{-1}), and n is flowability index [26]. Herschel Bulkley model means that all the gels possess yield stress; they need a minimum amount of stress to be applied to change the viscosity of the gels in pseudoplastic manner. From Table 5, it was found that the regression value of all gels was almost or equals to 1.0, illustrating that all the gels incorporated with SC of different extracts fits perfectly to this rheological modelling. The incorporation of petroleum ether, toluene, ethyl acetate, and acetone SC leaves extract into the carbopol gel had make the regression line to be perfectly 1.0000 from 0.9998 (for carbopol). In the other way, the regression for water SC leaves extract gel was reduced to 0.9995. However, the differences were very small, and all of them were still accepted as good regression that fits well to the Herchel Bulkley modelling. Regarding the yield stress value, it was found that toluene SC leaves extract gel had the lowest, while water SC leaves extract gel had the highest yield stress. This means more shear stress (at least 342.6 Pa) was needed to start producing shear rate of 1 s^{-1} of the water extract, but for toluene SC leaves extract gel, only 248.5 Pa is needed. Oral environment

which was exposed to very high shear stress and rates due to oral movement will become one of the challenges to develop mucositis gel that can last longer at the mucosa. Therefore, gels with high yield stress are more preferable, and in this case, is water SC leaves extract gel. Regarding consistency factor, which was denoted with k(Pa sn) indicates the gels consistency as a pseudo-plastic fluid.

From Table 5, it was found that all SC leaves extract gel decreased in consistency factor compared to plane carbopol gel, and the least consistency factor goes to water SC leaves extract gel. The gel with the highest consistency factor was ethyl acetate SC leaves extract gel. Regarding the flow behaviour index denoted by n, it was found that all n values show reading below than 1. The n value of less than 1 illustrates that the gels are pseudoplastic (shear thinning), while n = 1 illustrate the Newtonian behaviour. If n > 1, it means the gel is shear thickening (dilatant) [27-29]. The value of n for all the gels were almost the same, and the main point derived from here was all of them were pseudoplastic with shear thinning properties. Table 6 indicates the release profiles of all the SC leaves extracts gels. It was found that ethyl acetate had the highest permeation rate flux, followed by petroleum ether, toluene, acetone, and water extract. However, there is no significant difference between permeation flux of water extract and petroleum ether SC leaves extract gel and between water extract and toluene SC leaves extract gel ($p > 0.05$). The same goes to permeability coefficient, where ethyl acetate SC leaves extract gel was found to be the highest value, but water SC leaves extract gel was found to be the lowest value.

Table 7 demonstrates the texture profiles of all the SC leaves extract gels. All the texture profile properties; hardness, cohesiveness, adhesiveness, and springiness of the gel were applied based on the basic concept [30]. It was found that plane carbopol gel was found to be the hardest, but not significantly different ($p > 0.05$) from petroleum ether, toluene, ethyl acetate, and acetone SC leaves extract gels. While water SC leaves extract gel was found to be the softest, but not statistically significant difference from toluene, ethyl acetate, and acetone SC leaves extract gels. In term of cohesiveness, it was found that al the gels were not statistically significant difference from each other, meaning all of them are with the same cohesiveness. Springiness, which was found as how resilient or elastic the gels are had shown that plane carbopol, petroleum ether, toluene, ethyl acetate, and acetone SC leaves extract gel had statistically not significantly different ($p > 0.05$) value from each other, while water SC leaves extract gel is not statistically significant different ($p > 0.05$) from plane carbopol, petroleum ether, ethyl acetate, and acetone SC leaves extract gels. Regarding adhesiveness, which was tested to identify the gels adhesion on the bovine mucosa, it was found that all the gels were not significantly different from each other ($p>0.05$) except from plane carbopol and acetone SC leaves extract gel.

Total phenolic contents in S. cumini (L) were determined by Folin–Ciocalteu (F–C) method using Gallic acid as the standard. The absorbance values obtained at different concentrations of Gallic acid were used for the construction of the calibration curve. Total phenolic content of the extracts was calculated from the regression equation of calibration curve ($Y = 0.0001x$; $R2 = 0.9963$) and expressed as mg Gallic acid equivalents (GAE) per gram of sample in dry weight (mg/g).

Conclusion

It can be concluded that the total phenolic and catechin content is highest when SC leaves were extracted using Soxhlet apparatus using ethanol as solvent. On the other other hand, epicatechin content is highest when extracted using SFE with carbon dioxide is used as solvent at 150 bar pressure. Water SC leaves extract gel had the best rheological profile to a certain extent (in term of rheological profiles).

Even though the release profiles had shown that water extract had low permeability coefficient, it is statistically different in term of permeation rate flux from other gels. Regarding texture profile analysis, it was found that almost all the gels has shown not statistically significant difference except for springiness where water extract is a little bit low value.

Acknowledgments

The authors would like to express their appreciation to Faculty of Pharmacy and Faculty of Dentistry International Islamic University Malaysia (IIUM), as well as Department of Pharmaceutical Technology, Faculty of Pharmacy University College MAIWP International (UCMI) for their kind assistance in completing this study. Special thanks were also extended to Supercritical Fluid Center in Faculty of Food Science and Technology Universiti Putra Malaysia (UPM) as well as Malaysian Cocoa Board, Nilai Negeri Sembilan Malaysia for contributing and making this research a success.

Funding

This work was funded by the IIUM Research Grant Collaboration: SRCG20-022-0022 and University College MAIWP International TASREF Grant: UCMI/TNCPP/RMC/Geran/2022(40).

Authors' Contributions

Susi Sukmasari and Mohammad Nasrin Abdul Rahman contributed to the research design and planning, while Abdul Almonem Doolanea, involved in supervising the project. Nur Zakirah Mezan, Azyyati Mohammad Muzafar Shah, and Puteri Izz Khayrin Maghzan involved in conducting this research directly. All authors evaluated the data collected and contributed to the final manuscript. Mohd Hafiz Arzmi helps in editing this manuscript.

Conflict of Interest

The authors declare that no conflict of interest arises in this manuscript.

***Orcid*:**

Susi Sukmasari:
https://orcid.org/0000-0002-1955-0681
Mohammad Nasrin Abdul Rahman:
https://orcid.org/0000-0002-9366-6439
Abd Almonem Doolaanea:
https://orcid.org/0000-0002-8839-5048
Mohd Hafiz Arzmi:
https://orcid.org/0000-0002-9470-6412
Nur Zakirah Mezan:
https://orcid.org/0009-0009-2845-725X
Azyyati Mohammad Muzafar Shah:
https://orcid.org/0009-0001-8291-5540
Puteri Izz Khayrin Maghzan:
https://orcid.org/0000-0003-1725-2290

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How to cite this article: Susi Sukmasari, Mohammad Nasrin Abdul Rahman, Abd Almonem Doolaanea, Mohd Hafiz Arzmi, Nur Zakirah Mezan, Azyyati Binti Mohammad Muzafar Shah, Puteri Izz Khayrin Maghzan, Elucidation profile analysis syzygium cumini extract to be developed as oral anti-mucositis gel. *Journal of Medicinal and Pharmaceutical Chemistry Research*, 2024, 6(12), 1888-1904.

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