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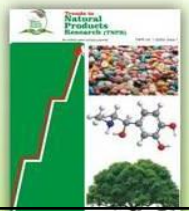

Evaluation of *Dacryodes edulis* Cream Formulations Against Some Causative Agents of Skin Infection

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Abstract
Dacryodes edulis is traditionally used in treating skin infections, wounds, parasitic worms, acute malaria, elephantiasis, and as an astringent. The global integration of medicinal plants into new pharmaceutical products is significantly increasing for improved health and wellbeing of man. This study formulated creams from the leaf extract of *D. edulis* following standard procedures and assessed the organoleptic properties, density, extruding time, spreading time, pH, diffusion rate, globule size, viscosity, antimicrobial, stability, and sub-acute toxicity using mice. The smooth formulated creams vary from light green to dark green in colour with density of 0.90 ± 0.02 to 0.95 ± 0.02 g/cm^3, extruding time of 5.57 ± 0.64 to 5.87 ± 0.78 sec, spreading time of 6.09 ± 0.07 to 7.49 ± 0.05 sec, pH of 3.46 ± 0.09 to 4.52 ± 0.08, diffusion rate of 1.58 to 3.33 mm/hr, globule size of 29.12 ± 15.00 to 53.21 ± 35.02 µm, and viscosity of 360.00 ± 16.33 to 1815.00 ± 148.49 mPa-s. The microbial inhibition zones (mm) were 11.0 ± 1.0 to 27.0 ± 1.0 for bacteria and 15.7 ± 0.6 to 22.0 ± 2.0 for fungi. The creams were stable at a lower temperature (29 ± 4 ºC) for 120 days. The skin of the mice showed no oedema or erythema when the cream formulations were applied. FDe1 had completely acceptable physicochemical properties, active against some microorganisms causing skin infections, and could be improved for commercial application.

Keywords
Dacryodes edulis, Creams, Physicochemical, antimicrobial, Toxicity

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Introduction

The skin, which composed of the epidermis, dermis and hypodermis layers (Yousef *et al*., 2019), is the largest organ of the body, accounting for about 15 percent of the total adult weight (Kanitakis, 2002). It protects the body against physical, chemical, and biological assailants; it also prevents excess water loss and acts as thermoregulator (Kanitakis, 2002). Skin infections are caused by bacteria, fungi, viruses, parasites, stings and bites (Colette and Ben, 2001; Kumar *et al*., 2007). *Staphylococcus aureus* is the commonest etiologic agent of boils, carbuncles, breast abscess, and different skin infections including infantile-impetigo and folliculitis (Cogen *et al*., 2008; Ratnam *et al*., 2017). *Staphylococcus aureus* is difficult to eradicate in the deeper skin layers, sweat gland, sebaceous gland, and the hair-follicles by everyday washing and scrubbing with antiseptic soaps (Cogen *et al*., 2008). *Pseudomonas aeruginosa* is known to cause folliculitis (Ratnam *et al*., 2017). Fungal infections of the skin, hair and nail are due to colonization of the keratinized layers of the body by organisms in the genera *Trichophyton*, *Microsporum* and *Epidermophyton* (Sultan *et al*., 2020). However, the genus Candida and non-dermatophytic moulds in the genera-*Fusarium*, *Scopulariopsis* and *Aspergillus* may also cause such infections (Lakshmipathy and Kannabiran, 2010; Farahmand *et al*., 2016). Tinea pedis (athlete's feet), Tinea cruris (groin), Tinea unguium (onychomycosis: nails), Tinea barbae (beard) and Tinea incognito (skin) are caused by *Trichophyton rubrum*, *T. mentagrophytes* and *Epidermophyton floccosum*, while tinea faciei (face) and tinea capitis (scalp) are also caused by *T. rubrum* and *T. mentagrophytes* (Starova *et al*., 2010; Sharma *et al*., 2015). In 2010, dermatophytes affected about one billion people globally (Vos, 2012). The infections are mostly common in developing countries due to poor hygienic conditions, close proximity to animals, poor socio-economy and the climatic support of the growth of dermatophytes (Sharma *et al*., 2015). According to British Association of Dermatologists (2015), severe consequences from skin infections are intolerable itching, discolouration and disfigurement, while inflammation of other tissues and internal organs may result to mental illness causing severe depression, social isolation, and even suicide (British Association of Dermatologists, 2015). Pathetically, despite the availability of the wide range of antifungal drugs for therapeutic purposes, relapse of diseases after treatment has been extensively reported (Perlin *et al*., 2015; Yubhisha *et al*., 2017).

Topical drug delivery system are dosage forms prepared for administration to the skin for local action, and the active components remain on the skin surface, or infiltrate the epidermal layers, and may get to the dermis, but not into the blood circulatory system. Contrarily, transdermal drug delivery system (transdermal patches) is systemic, because the drug traverses through the different layers of the skin to deliver the active ingredient(s) into the general blood circulation by different mechanisms, based on the composition and method of fabrication (Murthy and Shivakumar, 2010). Topical formulations are applied to a specific site on the outer surface of the body to treat local dermatological conditions. The absorption takes place through sweat glands, hair follicles, sebaceous gland, and the stratum corneum (Gidwani *et al*., 2010). Semi-solid topical formulations are collodions, foams, pastes, gels, ointments and creams (Murthy and Shivakumar, 2010; Chen, 2014). However, creams are frequently preferred over other topical preparations because they are less irritating and easier to apply. Also, they do not need complicated application procedures, thus circumvents the risks and inconveniences of intravenous drug delivery. According to Kranthi *et al.* (2011) creams are appropriate for patients with sensitive or dry skins that require a non-irritating, and non-drying formulation. Herbal creams are products that possess desirable physiological activities such as healing, smoothing, enhancing and conditioning properties of natural composition (Akash *et al*., 2015). The incorporation of medicinal plant materials into the modern pharmaceutical dosage forms is gaining much importance (Vijitha, 2013), and the demands for herbal topical formulations are increasing rapidly. It is generally known that plant parts used for topical preparations contain varieties of properties such as antioxidant, anti-inflammatory, emollient, antikerolytic, antiseborrhatic, and antibacterial activities (Aswal *et al*., 2013). Yadav and Yadav (2015) however stressed the advantages of herbal topical preparations have been for their non-toxic nature and reduced allergic reactions.

Dacryodes edulis (G. Don.) H. J. Lam (family: Burseraceae) is known as African plum or African pear. It is an evergreen tree that originated from Africa and is widely distributed in West and Central Africa (Burkill, 2004). Traditionally, the leaves and bark of *D. edulis* are used as antihelmintics, for treating diarrhea, dysentery, leprosy, and for clearing pregnancy stretch mark (Okwu and Nnamdi, 2008). In addition, the leaves were reportedly eaten raw with kola nut as an anti-emetic; the leaf sap is used for treating ear problems and the leaf decoction is for treating fever (Orwa *et al*., 2009). The fruit, leaf, bark and resin of *D. edulis* are

locally used in treating wounds, skin diseases, parasitic worms, elephantiasis, acute malaria, tonsillitis, and as astringent (Zofou *et al*., 2011; Omonhinmin, 2014; Adeniji *et al*., 2018); while its wood charcoal is used for treating eye disorder (Egbe *et al*., 2012). Furthermore, its pulp oil, avocado pulp, palm kernel oil and some spices are used together for skin smoothening while the pulped bark is for cicatrizing wounds (Burkill, 2004; Erhenhi *et al*., 2016). The resin exudate of *D. edulis* used singly or mixed with local oils (for example, palm oil) and applied topically to the skin is for treating ectoparasitic infection; and also, the leaf extract is used for dressing cuts, bruises and wounds (Omonhinmin, 2012). Moreover, the fruit, leaf and bark of *D. edulis* have been reported to contain phytochemicals such as tannins, saponins, flavonoids, alkaloids, cardiac glycosides, and anthraquinones (Udeme *et al*., 2013; Anyam *et al*., 2015; Aponjolosun and Fasola, 2022). The main components of the leaf essential oil were reported as elemol, caryophyllene oxide, trans-carveol and spathulenol, while p-cymene, α-thujene and β-phellandrene were abundant in the stem-barks and resin essential oil (Riwom *et al*., 2015). The plant has also been reported for its antioxidant (Oboh *et al*., 2015), antimicrobial (Anyam *et al*., 2015; Oyetunji and Opeyemi, 2017), and hepatoprotective activities (Noghayin *et al*., 2015).

Majority of people in the developing countries still prefer herbal medicine to some modern drugs for some reasons such as resistance of microbes, allergic reactions, fake products, high cost and scarcity of drugs especially in rural areas, as well as their socio-cultural biases about alternative medicine. Candidly, the challenges with the use of many therapeutic herbs are their crude unappealing forms, as well as their varied, inconsistent prescriptions, unlike the conventional drugs that are standardized. This necessitates the formulation and enhancement of some of these active herbal extracts into attractive forms with uniform dosages. Consequently, this research work was to formulate creams from leaf ethyl acetate fraction of *D. edulis* and assess their physicochemical properties, toxicity determination and antimicrobial capabilities against selected microorganisms causing skin infections.

Materials and Methods

Plant material collection, identification and Preparation

Dacryodes edulis leaves were collected within the University of Ibadan, Ibadan, Nigeria. They were authenticated by Mr. D. P. O. Esimekhuai and deposited with a voucher number (UIH 22488) at the University of Ibadan Herbarium (UIH). The leaves (Plate 1) were thoroughly washed with distilled water, air-dried for two weeks, and then milled. The pulverized sample (1 kg) was macerated in 3 L of methanol (BDH, England) for forty-eight hours. The liquid extract was decanted and filtered with Whatman filter paper No. 1. The filtrate was concentrated in a rotary evaporator (Heidolph Laborota, Germany), dried with a freeze dryer (Gallenkamp, UK), and successively partitioned with n-hexane and ethyl acetate. The ethyl acetate fraction was concentrated, dried and kept in an air-tight container until use.

Plate 1: Leaves and fruits of *Dacryodes edulis* (*var. edulis*)

Cream formulation

The aqueous cream BPC, which was the base for the formulations, was prepared by dissolving chlorocresol (0.1 % $^{w}/_{w}$) in warm distilled water (69.9 % $^{w}/_{w}$) in a beaker, poured into hot melted wax (emulsifying ointment: 30 % $^{w}/_{w}$) in a crucible, and stirred continuously until cold (BPC, 1979). Equal quantity of the humectant (propylene glycol: 10 % $^{w}/_{w}$) was separately mixed with the varied concentrations of the ethyl acetate fraction of *D. edulis* leaf (2.5, 5 and 10 % $^{w}/_{w}$) and afterward incorporated into the base (87.5, 85 and 80 % $^{w}/_{w}$ respectively) by continuous stirring until satisfactory products were formed. The formulated creams were coded FDe1, FDe2 and FDe3 respectively

Physicochemical assessment of herbal cream formulations

The organoleptic properties, density, extruding time, spreading time, pH, diffusion, globule size and viscosity of the herbal creams were determined as detailed below.

Visual assessments of colour, odour and texture of the formulated creams were done and observations recorded. The density was determined by taking the

weight of an empty 2 mL syringe, then filled with cream and re-weighed, and the cream's density was calculated using equation 1 below:

$$\text{Density}(g/cm^3) = \frac{(W2 - W1)}{V} \quad \text{..... Equation 1}$$

Where W1 is the weight of the syringe only,
W2 is the weight of the syringe and cream,
V is the volume of the cream.

Cream extruding time was determined by filling a syringe (2 mL) with the cream, and force was exerted at the plunger to extrude the cream from the syringe. The time taken to empty the syringe was recorded (Aponjolosun *et al*., 2023).

Spreading time was experimented by placing a cream (0.3 g) on a cleaned slide, covered with another cleaned slide, and a weight (140 g) was put on the slides for five minutes to have a uniform spread. The upper slide was moved along the lower slide and the time taken to separate the covered slides was recorded (Awad *et al*., 2015).

The pH of the creams was determined by a pH meter (Jenway, UK) at 25 ± 2 ºC. The electrode was dipped into each cream sample after calibration and average value of four measurements was determined.

Melted nutrient agar (20 mL) was poured and allowed to set in a glass Petri dish. It was flooded with 5 % $^{w}/_{v}$ Iron III chloride hexahydrate and the excess solution was drained off and air-dried. Three holes, bored into the agar by a 6 mm cup borer, were filled with the cream sample and incubated at 37 ºC. The diameters of the diffused cream were measured at various times (1-40 hours), the mean was calculated, values were plotted on a graph and the slope of the graph was determined (Femi-oyewo *et al*., 2013).

Globule sizes for the creams were determined using the microscopic method. The formulated creams were stained with crystal violet to create contrast between hydrophilic and hydrophobic components and thinly smeared on glass slides. Microscopic pictures were taken at x400 magnifications with a digital microscope, VJ-2005 DN model Bio-microscope®. The globule sizes of one hundred particles were randomly determined using TS View CX Image® Software, version 6.2.4.3 and Motic Image 2000, China.

The viscosity of each formulated cream was determined with Brookfield viscometer (VT 181, Karlsruhe, Germany) at 28 ± 2 ºC using spindle number 7. The spindle was lowered perpendicularly into the cream without touching the bottom of the plain tube and readings were recorded. In addition, the viscosity of each cream at varying rotational speed (2.5, 4, 5, 10, 20, 50 and 100 rpm) were done and plotted to describe the rheological pattern (Ajala *et al*., 2016).

In vitro antimicrobial test

Two typed bacteria: *Staphylococcus aureus* (ATCC 2785) and *Pseudomonas aeruginosa* (ATCC 29213); two clinical bacteria: *S. aureus* and *P. aeruginosa*; and three clinical fungi: *Trichophyton rubrum*, *Epidermophyton* sp. and *Candida albicans* were obtained from Department of Medical Microbiology, College of Medicine, University College Hospital (UCH), Ibadan. Agar well diffusion technique with Sabouraud Dextrose Agar (SDA, Biolife Lab., Italy) was used for the antimicrobial test with a sterile cork borer (6 mm) that made six wells into the agar. Varied concentrations of *Dacryodes edulis* ethyl acetate fraction (12.5, 25, 50, 100 and 200 mg/mL) were employed. Also, each cream (0.5 g) was filled into a well, allowed to stand and diffused for 30 min., incubated for 24 h at 37 ºC for bacteria and 48 h at 25 ºC for fungi. Ethyl acetate, Amoxillin tablet (Pacmentin-625, Medicef Pharma, India) and Ketoconazole tablet (Mycozoral, Ciron Drugs, India) were used as the controls for the antimicrobial test of the plant fraction, while aqueous cream BPC (base), Tydineal cream (Adams Pharmaceutical, China) and Mycozoral cream (Ciron Drugs, India) were used as the controls for the *D. edulis* formulated creams. The zones of inhibition were measured and recorded (Junaid *et al*., 2006; Ajala *et al*., 2016).

In vivo antibacterial test

Twenty-five male albino mice (15 – 20 g) were procured from the Animal House of Faculty of Veterinary Medicine, University of Ibadan. They were divided into five groups of five animals at the Animal House of Veterinary Anatomy Department of the same institution. Ethical approval for animal experiment was obtained from the University of Ibadan Animal Care and Use Research Ethics Committee (UI-ACUREC/App/2016/033). The Guide for the Care and Use of Laboratory Animals according to Garber *et al*. (2011) were followed for the animal experiments. They were acclimatized for two weeks and were also given food and water *ad libitum* throughout the experimentation. Intradermally, 0.5 mL of *Staphylococcus aureus* (a log-phase culture of dilution 10^{-8} CFU) was injected into the shaved marked out lateral part of each mouse. The treatment of the mice commenced after 24 h of inoculation. In each group, 200 mg of FDe1, FDe2, FDe3 and Tydineal cream (reference cream) were topically applied once daily on the mice for three days while the untreated group was the control. The mice were sacrificed on the fourth day by quick cervical dislocation and decapitation. The treated site of the skin of each mouse was excised and put inside 2 mL sterile peptone water. Serial dilution was done by adding 0.1 mL from the peptone water to 9.9 mL sterile peptone water, and from which 0.2 mL was cultured on Mannitol Salt Agar (MSA,

Biowark Lab., Pune, India) and incubated for 24 h at 40 - 45 ºC. Viable count of *S. aureus* was determined with a colony counter (Stuart Scientific Ltd, Great Britain) and the percentage bacteria survival was calculated (Gisby and Bryant, 2002).

Stability studies of the cream formulations

The stability studies of the formulated creams for 120 days were determined by two analyses: the viscosity and the organoleptic properties of the creams (that is, colour, odour, and texture) when stored under different temperatures of 29 ± 4 ºC, 0 ºC and 46 ºC

Dermal toxicity test

Four-week-old twenty male albino mice (7 - 12 g) were procured, confined into four cages of five mice per cage and acclimatized for two weeks. The animals were given food and water *ad libitum* prior and throughout the period of experimentation in the above-mentioned animal house. The side of each mouse (2 cm diameters) was clipped free of fur and a cream (200 mg) was topically applied on it for twenty-one days while the untreated group served as the control. The behaviour and the skin of the mice were keenly observed during the experiment. The mice were sacrificed by quick cervical dislocation and decapitation and the sites of the skins were harvested and kept inside 10 % formalin. Serial sections of 5 µm thickness of the skins were made after paraffin embedding, block making, staining with haematoxylin and eosin, and were examined microscopically (OCED, 2002; Kamkaen *et al*., 2007).

Statistical analyses

Microsoft Office Excel software (2016) was used to analyse the data of physicochemical and antimicrobial properties of the cream. Prism Software (Graphpad) package 5.00 was used to analyse the data of viscosity and globule size. The data were tested ($p < 0.05$) using unpaired student's t test, analysis of variance (ANOVA) and Turkey Kramer's multiple comparison tests.

Results

The physicochemical properties of the formulated creams of *D. edulis* are presented in Table 1. The herbal creams were oil-in-water (O/W) non-greasy, viscous and water washable preparations with pleasant outlook. The colours of the cream formulations deepened as the plant extract concentrations increased. The densities were influenced by the quantity of base and the presence of the humectant, and was in the order, FDe1 > FDe2 > FDe3. Likewise, the creams showed the same order for the extruding time and spreading time which occurred within seconds. The pH was between 3.25 to 4.52 and the rate of diffusion was ranked FDe1>FDe2>FDe3. The globule sizes of the creams were less than 100 µm with a range of 29.12 to 95.99 micrometre. The creams had high viscosity with significant difference between FDe3 and others. The rheological patterns of the formulated creams are shown in Figure 1. The rheology was non-Newtonian with pseudoplastic outlook. The graphs of FDe1 and FDe2 are closer and higher than FDe3 as influenced by their viscosity values.

Table 1. Physicochemical properties of *Dacryodes edulis* creams

Parameters	FDe1	FDe2	FDe3	EAFDe
EAFDe composition (%)	2.5	5.0	10	100
Colour	Light green	Green	Dark green	Dark green
Density (g/cm^3)	0.95 ± 0.02	0.92 ± 0.01	0.90 ± 0.02	NA
Extruding time (sec.)	5.87 ± 0.78	5.73 ± 0.65	5.57 ± 0.64	NA
Spreading time (sec.)	7.49 ± 0.05	6.53 ± 0.07	6.09 ± 0.07	NA
pH	4.52 ± 0.08	3.24 ± 0.05	3.46 ± 0.09	3.59 ± 0.06
Diffusion rate (mm/hr)	3.33	1.92	1.58	NA
Globule size (µm) *	53.21 ± 35.02	95.99 ± 75.56	29.12 ± 15.00	NA
Viscosity (mPa-s) at 50 rpm	1815.00 ± 148.49	1725.75 ± 239.36	360.00 ± 16.33	NA

Mean ± SD, n = 4, '*****' means n = 100, FDe1, FDe2, FDe3 = formulated creams, EAFDe = ethyl acetate leaf fraction of *D. edulis*, NA = not applicable.

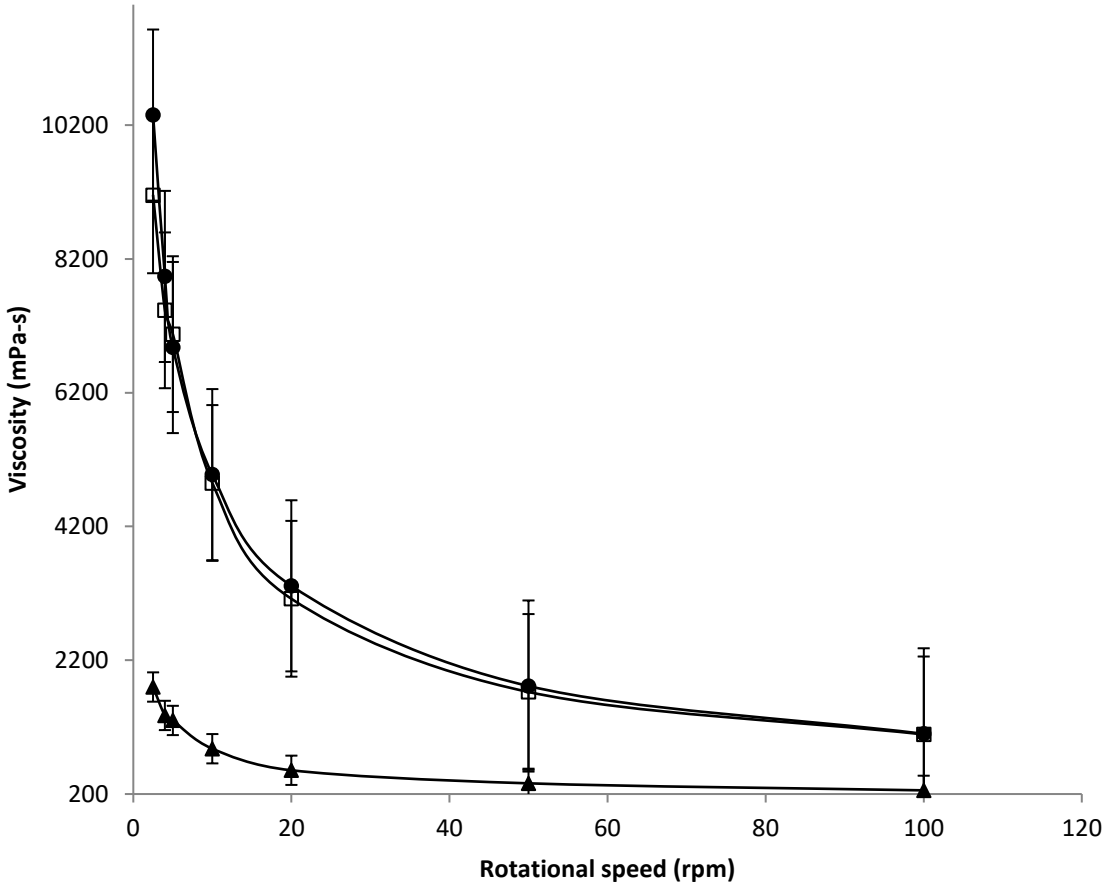

Figure 1: Rheological profiles of *Dacryodes edulis* creams
□ FDe1 □ FDe2 □FDe3
FDe1, FDe2, FDe3 have 2.5, 5, 10 % ethyl acetate leaf fraction of *D. edulis* respectively

The antimicrobial properties of *D. edulis* leaf ethyl acetate fraction are presented in Table 2. Also, the activity of the plant fraction at 200 mg/mL was higher in *P. aeruginosa*, *P. aeruginosa* (ATCC 29213), *T. rubrum* and *C. albicans* than the positive controls-amoxicillin and ketoconazole drugs. The antimicrobial properties of the formulated creams are presented in Table 3. The creams showed concentration-dependent activity in the order, FDe3>FDe2>FDe1. *However,* formulations *with lower concentrations of D. edulis* fraction *were inactive against T. rubrum and Epidermophyton species.* The two reference creams showed highest antimicrobial activities in the experiment than the cream formulations.

Table 2. Antimicrobial properties of *Dacryodes edulis* leaf ethyl acetate **fraction**

Microorganism	Extract concentration (mg/mL)					Amoxillin	Ketoconazole
	12.5	25	50	100	200	20 µg/mL	50 mg/mL
	Zones of inhibitions (mm)						
Staphylococcus aureus	10	10	12	12	14	14	NA
Staphylococcus aureus$^{ATCC\ 2785}$	-	-	10	12	14	16	NA
Pseudomonas aeruginosa	14	16	18	20	22	14	NA
Pseudomonas aeruginosa$^{ATCC\ 29213}$	-	10	12	14	20	16	NA
Tricophyton rubrum	-	10	12	18	20	NA	16
Epidermophyton sp.	-	-	-	10	14	NA	16
Candida albicans	-	10	10	12	26	NA	16

ATCC = American Type Culture Collection. - = No inhibition. NA = Not applicable.

Table 3. Antimicrobial properties of *Dacryodes edulis* creams

Microorganisms	Zones of inhibition (mm) (Mean ± SD, n = 3)				
	FDe1	FDe2	FDe3	Tydineal	Mycozoral
Staphylococcus aureus	11.0 ± 1.2	12.0 ± 0.0	27.0 ± 1.0	33.7 ± 0.7	NA
Staphylococcus aureus $^{ATCC\ 2785}$	12.0 ± 0.0	-	25.0 ± 1.0	35.7 ± 0.6	NA
Pseudomonas aeruginosa	12.6 ± 1.2	-	22.0 ± 2.0	33.7 ± 0.6	NA
Pseudomonas aeruginosa $^{ATCC\ 29213}$	11.0 ± 1.0	18.0 ± 2.0	23.0 ± 1.0	33.7 ± 0.6	NA
Tricophyton rubrum	-	-	17.7 ± 0.6	NA	25.7 ± 0.6
Epidermophyton sp.	-	-	17.0 ± 1.0	NA	27.7 ± 0.6
Candida albicans	15.7 ± 0.6	18.0 ± 0.0	22.0 ± 2.0	NA	27.7 ± 0.6

FDe1, FDe2, FDe3 are creams containing 2.5, 5, 10 % ethyl acetate leaf fraction of *D. edulis* respectively. ATCC = American Type Culture Collection. - = No inhibition. NA = Not applicable.

The *in vivo* antibacterial activity of *D. edulis* cream is presented in Table 4. There was concentration-dependent activity of the formulated creams on *S. aureus* (FDe3 > FDe2 > FDe1). The untreated mice and those treated with the cream base showed significant survival of *S. aureus* unlike those treated with the formulated creams. In addition, there were insignificant differences in the survival of the *S. aureus* in the mice treated with the formulated creams but significant when compared with Tydineal cream.

Table 4. Effect of *Dacryodes edulis* creams on mice skin injected with *Staphylococcus aureus*

Parameters	*D. edulis* fraction (%)	Bacteria survival (%)	Bactericidal effect (%)
FDe1	2.5	14.97	85.03
FDe2	5.0	14.79	85.21
FDe3	10	14.11	85.89
Tydineal cream	NA	12.07	87.93
Untreated mice	NA	ND	ND

FDe = cream containing ethyl acetate leaf fraction of *D. edulis*. NA = Not applicable. ND = Not determinable because growth was too numerous for viable count.

The mean viscosity for FDe1 stored at room temperature (29 ± 4 ºC) had the highest value of mean viscosity (5060 ± 1590 mPa-s), while the cream stored at high temperature (46 ºC) produced the least (4085 ± 722.4 mPa-s). Likewise, for FDe2, the cream stored at room temperature (29 ± 4 ºC) had the highest value of mean viscosity (4939 ± 1398 mPa-s), while the cream stored at high temperature (46 ºC) was the least (4050 ± 1108 mPa-s). However in FDe3, the cream stored at cold temperature (0 ºC) had the highest value of mean viscosity (3705 ± 1107 mPa-s), while the cream stored at high temperature (46 ºC) produced the least (3134 ± 780.4 mPa-s) (Figure 2).

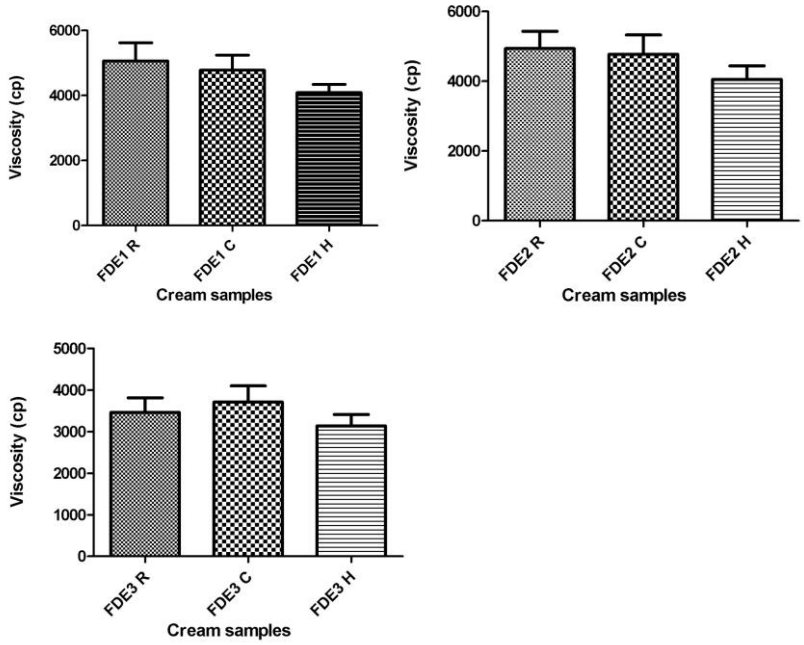

Figure 2. Mean viscosity of *Dacryodes edulis* creams of 120 days at different temperatures

FDE1 = 2.5 % leaf ethyl acetate fraction of D. edulis cream, FDE2 = 5 % leaf ethyl acetate fraction of D. edulis cream, FDE3 = 10 % leaf ethyl acetate fraction of D. edulis cream, R = 29±4 ºC, C = 0 ºC, H = 46 ºC. 1cp =1mPa-s

In FDe1 and FDe2, the cream stored at room temperature (R) had the highest viscosity while the cream stored in a hot place (H) produced the least. However, in FDe3, the cream stored inside freezer (C) had the highest viscosity, while the cream stored in a hot place (H) gave the least value. However, there was no significant difference between the cream stored at room temperature (R), compared with the one stored inside freezer (C), likewise for R compared with H, and also for C compared with H, thus showing their stability. There were no observable changes in the state, colour, texture, and odour of all the formulated creams stored at 29 ± 4 ºC and 0 ºC. Moreover, there was no observable change in the state, texture, and odour of the cream stored at 46 ºC, but a gradual colour change (dark patches) was noticed from day 49 (Plate 2).

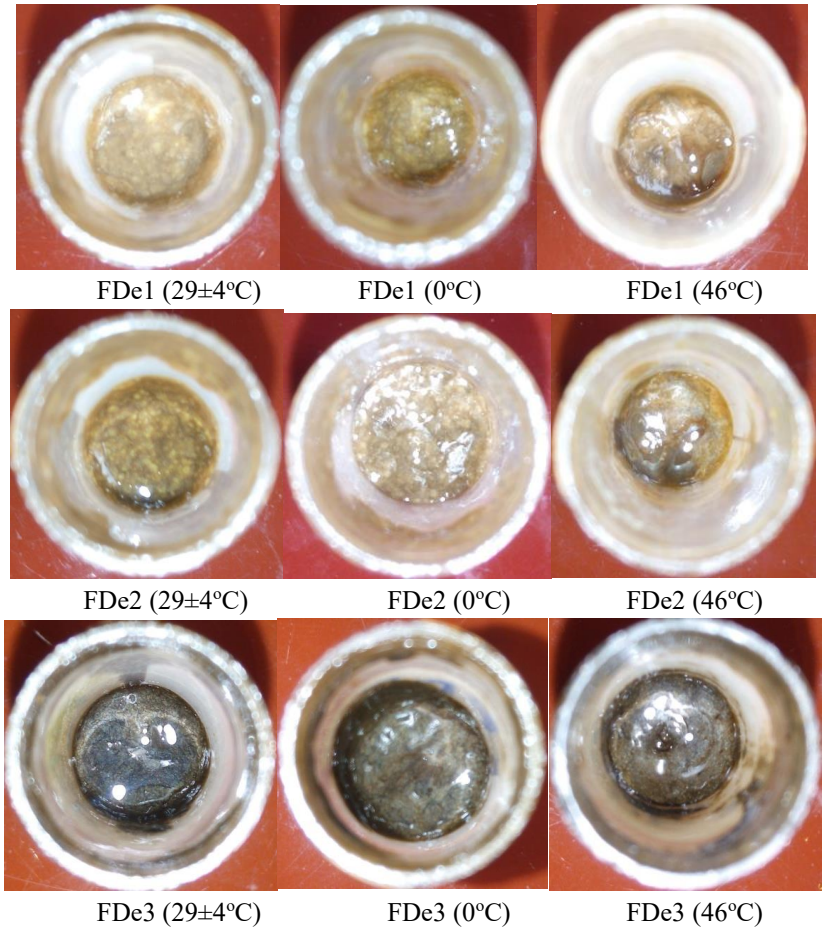

Plate 2. *Dacryodes edulis* creams at day 120 showing organoleptic stability profiles FDe1 = 2.5 % leaf ethyl acetate fraction of *D. edulis* cream, FDe2 = 5 % leaf ethyl acetate fraction of *D. edulis* cream, FDe3 = 10 % leaf ethyl acetate fraction of *D. edulis* cream.

The photomicrographs of the mice skin are shown in Figure 3. There was no behavioural abnormality, oedema, erythema or anomalous colour change in the newly grown furs of the mice in this study. Likewise, the microscopic examination of the mice skin tissues showed no visible lesions.

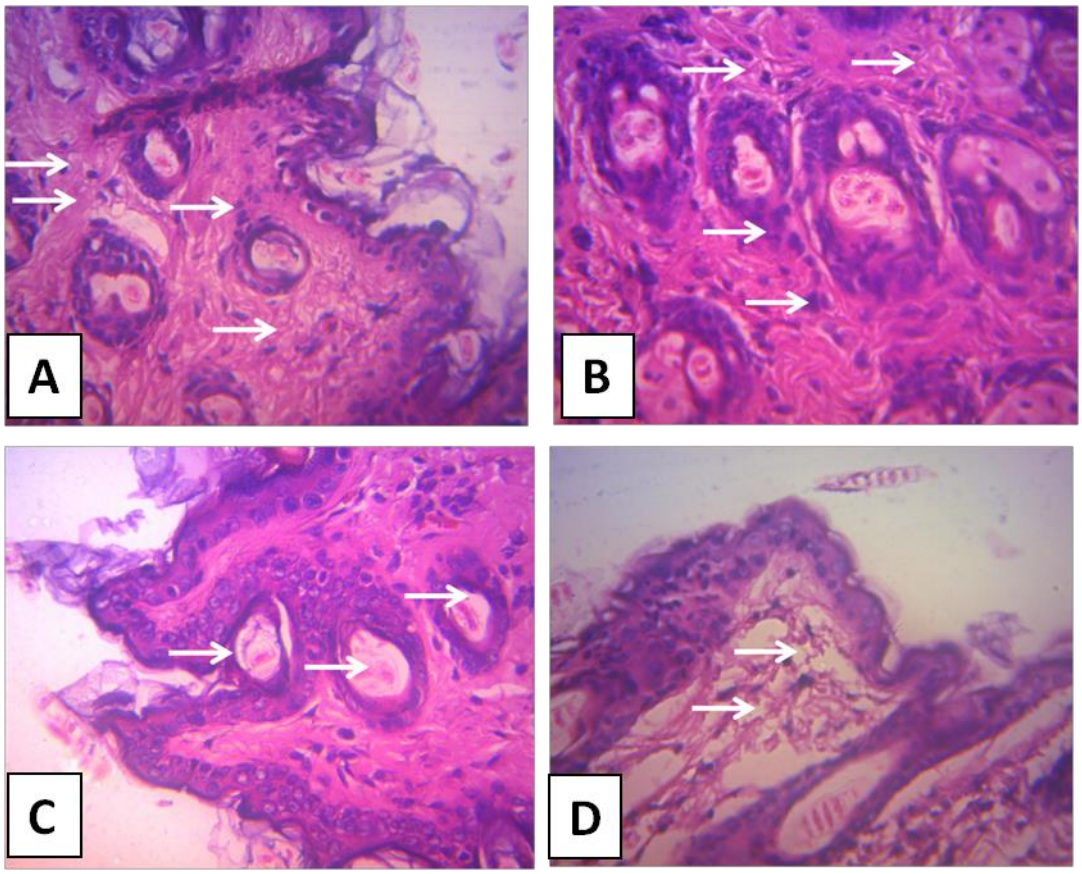

Figure 3. Photomicrographs of mice skins (x400) treated with *Dacryodes edulis* creams showing no visible lesions

A, B, C are mice skin treated with creams having 2.5, 5, 10 % ethyl acetate leaf fraction of D. edulis respectively while D is untreated mice skin. A = There is high density of hair follicle sections and sebaceous glands. There is a mild to moderate dermal cellular infiltration (arrows), especially within the dense collagen fibers and around the base of the hair follicles. B = There is a severe dermal cellular infiltration, especially around the base of the hair follicles (arrows). C = The follicle and sebaceous sections are dense within the collagen fibers. The hair follicle sections are prominent and appear enlarged (arrows). D = The dermal collagen is very sparse and loose (arrows). There are no lesions seen.

Discussion

Dacryodes edulis cream formulations were oil in water emulsions and these are the most commonly used semi-solid emulsions in topical delivery systems. Oil in water creams are commonly used because they supply moisture to the skin and also improve the skin condition by forming occlusive barrier on it (Gade *et al*., 2015). The prepared cream formulations therefore have potential for translational outcomes. In addition, the creams were smooth, appealing and shining with distinctive scent. The presence of humectant in the creams might have contributed to the shiny and attractive appearance. The attractive colour, smoothness and pleasant scent of the formulated creams could improve patient's compliance towards its use.

Extruding and spreading times were done as useful empirical tests to note the time required to extrude each cream from the tube and ensure spreading on the skin. Since all formulations extruded within and spreaded within seconds, they could serve parameters for user-friendliness of the products. If much time is required to extrude a cream, patients might not be encouraged to use it thus reducing patients' compliance and therapeutic efficacy. More also, the bioavailability efficiency of the formulated creams depends on their spreading value. According to Nayeem and Karvekar (2011), semi-solid formulations should spread easily without much drag nor produce friction in the rubbing process. The pH of the cream formulations tolled the line of the extract, FDe1 which had the least extract

concentration showed an acceptable pH of 4.52. This implies that only FDe1 is satisfactory with respect to pH. Before translational efforts can continue with the other cream formulations (FDe2 and FDe3), the need to adjust pH will be necessary. Till then, FDe1 with acceptable pH is considered as useful.

The maximum globule size for a conventional cream is 100 µm (Rolland, 1993). Hence, the formulated creams were within the globular size acceptable limit that could penetrate the stratum corneum to deliver their therapeutic function. Viscosity expresses the magnitude of internal friction in a fluid, therefore, in terms of consistency, the creams showed satisfactory properties. However, it was observed that the value of FDe3 was much lower when compared with FDe1 and FDe2. This was probably because of the quantity of the plant fraction used in FDe3. The rheological profiles demonstrated a non-Newtonian rheology, because as the rotational speed increased, the viscosity of all the creams decreased. Non-Newtonian behaviour is seen in some fluids such as butter, honey, saliva, and cosmetics (Schramm, 2005; Chhabra, 2006; Rao, 2007). However, creams are semi-solid pharmaceutical formulations which are generally non-Newtonian with pseudoplastic flow pattern. This is the reason why a cream application behaves as a solid on the skin surface until a force is applied before it can spread on the skin. This clearly distinguishes it from lotions which flow without the application of stress. In terms of rheology, the formulated creams displayed acceptable properties.

The antimicrobial activity of the plant fraction was concentration-dependent and at the highest concentration tested, there were significant inhibitions on all the microorganisms. The curative properties in medicinal plants are because of some plant secondary metabolites in them (Awad *et al*., 2015). The phytochemicals in the fraction of *D. edulis* leaf might have caused damage of some essential cellular components of the microorganisms, and hence their antimicrobial activities. Herbal medicine as an independent mode of treatment could be helpful in treating fungal infections (Farahmand *et al*., 2016). However, the ethyl acetate fraction of *D. edulis* has demonstrated self-sufficient ability to singly combat the tested fungi. Interestingly, the antimicrobial activities of the creams were somewhat consistent with the results from the plant fraction. The additives did not negatively affect the activity *of* the plant fraction in the creams. Moreover, *the* creams *showed improved antimicrobial properties than the plant fraction;* except at 200 mg/mL, where *the plant fraction* showed higher activity against *T. rubrum* and *C. albicans*. The reference creams had higher antimicrobial activity, and this could be because they are refined products, and probably the synergistic action of the multiple ingredients in Tydineal cream. Tydineal cream consists of ketoconazole, neomycin sulphate and clobetasol propionate while mycozoral cream consists of ketoconazole. The *in vitro* antimicrobial and *in vivo* antibacterial activity showed that *D. edulis* creams could be further studied and developed in treating skin infections such as boils, carbuncles, impetigo and folliculitis.

There were insignificant changes in the organoleptic properties of the creams stored under room temperature (29 ± 4 ºC) and cold (0 ºC) on day 120. However, significant changes of dark patches were observed in those stored at higher temperature (46 ºC) from day 49; therefore, the former showed stability while the latter showed degradation of products. This outcome was similar to Goncalves and Gobbo (2012) who developed cosmetic formulations from apple extracts of *A. occidentale*, and reported gradual darkening of the formulations stored between 40 ºC and 60 ºC after twenty-eight days. Derick (2000) explained phase separation, as a type of instability that occurs in emulsified systems, sometimes called creaming, resulting into reduction of viscosity and increase in liquefaction caused by time and temperature. Abdurahman and Rosli (2006) added that an emulsion with smaller particles have higher viscosity and hence decrease the rate of creaming.

Akhtar *et al*. (2011) reported that a change in temperature also has an indirect effect on the stability of an emulsified system, including creams. This occurs by changing the interfacial tension, viscosity, nature of surfactant, vapour pressure of the liquid phases and thermal agitation of the molecules. However, there was no phase separation in *D. edulis* creams stored at different temperatures (29 ± 4 ºC and 0 ºC), thus showing their stability for 120 days of observation.

The mean viscosity range for *D. edulis* creams stored at different temperatures was 3134 ± 780.4 – 5050 ± 1590 mPa-s. Generally, there were significant increases in the viscosities of *D. edulis* creams stored at different temperatures over time. Therefore, the stored creams showed rheopectic behaviour. This opposed Ajala (2014), who reported that there were insignificant changes in the viscosities of *Phyllantus amarus* creams at different temperatures over time. This might be due to the different plants and humectants used for the cream preparations. The observed stability of *D. edulis* creams could be because of the compatibility of the extracts with the base. Moreover, Huang *et al*. (2001) reported that small oil globules, high viscosity and compatibility of base with the active principles in plant extract, generally contribute to the stability of any cream.

Rawlins (2004) reported that temperature affects viscosity of fluids and semi-solids in an indirect relationship by the Arhenius equation. Therefore, this study supports that creams should be stored at

lower temperature (not more than 29 ± 4 ºC), in order to prolong stability and shelf life; because higher temperatures accelerate degradation.
An ideal topical product is one that achieves a concentration in the target tissue that is sufficient to produce a desired pharmacological reaction, has an acceptable safety profile, and leaves the skin free from injury (Laxmi and Pranita, 2014). The use of mice as model organisms to study human biology is predicated on the genetic and physiological similarities between mice and man (Perlman, 2016). Consequently, the formulated *D. edulis* creams could be regarded as a non-toxic topical application from the results of safety study in mice. However, for human commercial usage, irritation assessment on human skin is imperative (Nair *et al*., 2012).

Conclusion

The cream formulations of *Dacryodes edulis* have satisfactory physicochemical properties except for the pH of FDe2 and FDe3. The cream formulation containing 10 % ethyl acetate fraction of *D. edulis* leaf (FDe3) was the most potent against the tested microorganisms. In addition, all the creams were more stable at lower temperatures, hence should be stored in cool dry places. FDe1 had completely acceptable physicochemical properties, active against some microorganisms causing skin infections, and could be improved for commercial application.

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Authors' contributions

Research concept and study design-Aponjolosun B.S, Ajala T.O and Fasola T.R
Data collection, analysis and interpretation: Aponjolosun B.S and Ajala T.O
Study supervision: Fasola T. R
Study Co-supervision- Ajala T.O
Writing of manuscript draft: Aponjolosun B. S
Revision of manuscript: Ajala T.O, Fasola T.R
Approval of manuscript for submission: Aponjolosun B.S, Ajala T.O and Fasola T.R

Conflict of interest

No conflict of interest is associated with this work.

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