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Research Article

Anti-inflammatory Property of Gels Formulated using *Dacryodes edulis* Bark Ethanol Extract

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ABSTRACT

This work was done to assess the anti-inflammatory property of gels formulated using ethanolic extract of *Dacryodes edulis* bark. *Dacryodes edulis* bark was ground to coarse powder and macerated in ethanol for 48 h. It was filtered by straining using muslin cloth. The filtrate was dried for 12 h in a water-bath at 73±1oC and the dried extract was stored in an airtight container. The extract was evaluated for its phytochemical composition. The extract was evaluated for anti-inflammatory activity and skin irritation study. The gels were made by incorporating the extract into a gel base made of either carbopol or sodium carboxymethylcellulose (NaCMC) as the gelling agent. The gels were evaluated for anti-inflammatory activity, spreadability, pH, viscosity and physical appearance. The *Dacryodes edulis* bark ethanolic extract was found to contain flavonoids, tannins, reducing sugars, alkaloids, terpenoids, cardiac glycosides and saponins. The extract has good anti-inflammatory property. The gels formulations that contained propylene glycol as penetration enhancer showed higher anti-inflammatory activity than those without it. The gels prepared with carbopol as gelling agent exhibited higher anti-inflammatory activity than those formulated with NaCMC. There was no skin irritation by any of the formulations. The gels had good homogeneity and consistency with no phase separation. The pH ranged from 4.1 to 8.5, while the spreadability ranged from 0.9 to 1.9 cm. The viscosity was between 12,250 to greater than 20,250 mPas. Gels that displayed anti-inflammatory activity with good physicochemical properties were produced using *Dacryodes edulis* bark ethanolic extract.

Keywords: *Dacryodes edulis , anti-inflammatory activity, gels, viscosity, spreadability.*

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INTRODUCTION

Dacryodes edulis is native to West and Central African countries such as Nigeria and Cameroon. It is a fruit tree and is also called native pear, local pear, African pear, or bush butter tree (Onuegbu *et al*, 2011; Oyetunji and Opeyemi, 2017). It belongs to the family Burseraceae, and it is also known as ube in Ibo, eben in Efik, Safou in French, elemi in Yoruba, and orumu in Bini (Okwu and Nnamdi, 2008; Onuegbu *et al*, 2011). It attains a height of 18m and when the stem is injured or its portion excised, a gummy substance that is odoriferous is exuded (Okwu and Nnamdi, 2008). Its leaves, bark and resin are used traditionally medicine to treat infections, skin diseases, scabies, ringworm, fever, wound, pain and malaria (Miguel *et al*, 2017; Oyetunji and Opeyemi, 2017). Different parts of the plant posses antibiotic, antioxidant, anti-inflammatory, immune-stimulating, hypoglycemic and hypolipemic potentials (Miguel *et al*, 2017; Oyetunji and Opeyemi, 2017).

Inflammation serves as a protective and defense mechanism for the body. It is one of the reactions of vascular tissues to stimuli that causes it injury, like pathogens, irritants, damaged cells or by host proteins, and coagulation systems which are stimulated by microorganisms and damaged tissues (Sharma *et al*, 2015; Odoh and Ene, 2020). Classical symptoms associated with acute inflammation are redness, pain, local heat, and swelling (Furst *et al*, 2012; Sharma *et al*, 2015). In chronic inflammation, several mediators that are not salient in the acute response are released. Conditions that results in chronic inflammation such as rheumatoid arthritis causes pain and destruction of bone and cartilage that can lead to severe disability and mortality worldwide (Furst *et al*, 2012; Muhwana *et al*, 2020). Two primary goals are borne in mind when treating patients that have inflammation; symptoms relief and function maintenance, and retardation and halting of the process of tissue-damage (Furst *et al*, 2012). Inflammatory diseases and pain are managed using corticosteroids, non-

steroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics (Muhwana *et al*, 2020). Drugs for management of inflammation and pain are usually expensive and they produce severe adverse effects and some cause dependence (Muhwana *et al*, 2020). This necessitates the search for natural or herbal anti-inflammatory drugs which are usually safe and less expensive.

Topical applications of herbal drugs have gained relevant attention as a result of their prevalent use and they can be utilized as ointments, gels, creams, that are rubbed directly on the outer body surface (Kaushik *et al*. 2020). Topical or trans-dermal drug delivery is the delivery of drugs via the skin. It serves as a plausible alternative administration route to oral and parenteral routes. Administration of drugs via the topical route is non-invasive, extends duration of action, circumvents first pass metabolism, and produces constant plasma drug levels. It also results in reduction of frequency of dosing, reduction in drug untoward effects and toxicity, and enhancement of patient compliance (Bolla *et al*, 2020). Entrance of drugs and foreign compounds via the skin usually is blocked by stratum corneum. The use as penetration enhancers of ethanol and propylene glycol increases the transport of drugs via the skin. They enhance the diffusion of drugs via the skin by interacting and altering the complex structure of skin and thereby, increasing drug partition into different layers (Bolla *et al*, 2020). Several commonly used topical preparations such as creams, ointments, and lotions suffer from drawbacks such as being very sticky, making patient uncomfortable when applied and having less spreading coefficient requiring application with rubbing. They also have stability issues. As a result of the disadvantages associated with ointments and creams, the utilization of transparent gels has increased both in cosmetics and in pharmaceutical preparations (Khunt *et al*, 2012). Drugs are released faster directly to site of action from gels, notwithstanding its solubility in water, than from ointments and creams (Crowley, 2005; Kaushik *et al*. 2020). The duration the drug stays on the skin can be increased by topical application of gel and this may result in enhancement of the delivery and release of the active pharmaceutical ingredient at the site of application (Dantas *et al*, 2016).

Gels are colloids composed of 99% liquid by weight, of which the dispersing medium movement is limited by interconnecting three-dimensional network of particles or solvated macromolecules in the dispersed phase. Physical and/ or chemical cross-linking may be involved (Crowley, 2005; Khunt *et al*, 2012). Gels can also be defined as semisolids systems that are composed of suspensions that contain minute inorganic particles or macro-organic molecules interpenetrated by a liquid. Two-phase system gels have gel mass that contain network of tiny discrete particles. However, when the gel is consist of organic macromolecules that are evenly spread within a liquid without any clear demarcation between the dispersed macromolecules and the liquid, then it is a single-phase gel. Single-phase gels can be produced from natural gums or from synthetic macromolecules (Crowley, 2005).

The solubility of the ingredients contained by a gel system dictates whether it will be clear or turbid. The ingredients may be partially soluble or insoluble, or produce aggregates that disperse light. The gelling agents are used at concentration that is below 10% and often at 0.5 to 2.0% (Crowley, 2005). Single-phase gels are often used in pharmacy due to their semisolid state, high degree of clarity, ease of application, and ease of removal and use (Crowley, 2005).

This research was done to assess the anti-inflammatory activity of ethanolic extract from *Dacryodes edulis* bark and that of the gel produced using the extract.

MATERIALS AND METHODS

Materials: Carbopol (Loba Chemie. Pvt. Ltd, Delhi, India), sodium carboxymethylcellulose (BDH Chemicals Ltd Poole England), propylene glycol (Sigma–Aldrich St. Louis, USA), triethanolamine (Nice Chemicals Pvt. Ltd., Mumbai, India), carrageenan (Sigma–Aldrich St. Louis, USA), ethanol (May & Baker, Dagenham, England). Other reagents used were of analytical grades.

Collection of Sample: The bark of *Darcyodes edulis* was collected from Obiaruku area of Delta State, Nigeria on the 24th October, 2019.

Extraction of *Dacryodes edulis* bark: The collected barks were dried for eighteen (18) days and were size reduced to coarse form using a mortar and pestle. The coarse particles were milled to powder with a blender. The powdered bark was macerated in ethanol for 48 h with stirring at intervals and filtered by straining using muslin cloth. The filtrate was dried for 12 h using a water-bath at 73±1ºC. The extract's weight obtained was noted and equation 1 was used to calculate the percentage yield.

$$\%Yield = \frac{Wf\ x\ 100}{W} \ldots\ldots 1$$

Where W_f =final weight of the extract; W= weight of the dried bark

Table 1:
Composition of gel containing ethanolic extract of *Dacryodes edulis* bark

	Extract (g)	Carbopol (g)	NaCMC	Propylyne Glycol (g)	Triethanolamine (TEA)	Water (g) to
F1	-	0.34	-	-	0.4	35
F2	-	-	0.34	-	-	35
F3	1.35	0.34	-	-	0.4	35
F4	1.35	0.34	-	1.70	0.4	35
F5	1.35	-	0.34	1.70	-	35
F6	1.35	-	0.34	-	-	35
F7	1.35	-	-	-	-	35

Preparation of gel: The gel was prepared by adding carbopol to distilled water heated to 75ºC in a beaker. Another beaker was used to dissolve the extract in water and it was mixed with propylene glycol. It was stirred to until completely dissolved. The mixture was incorporated into the carbopol gel base. It was stirred continuously until a homogenous mixture without lumps was formed. Triethanolamine (TEA) was incorporated into the mixture and it was stirred properly without lumps. The other formulations were produced following the same process using the formula in Table 1 except that formulations that contained sodium carboxymethylcellulose (NaCMC) were prepared at room temperature.

Evaluation of Extract

Determination of solubility: The extract's solubility in different solvents was evaluated by dissolving it in warm distilled water, distilled water at room temperature, ethanol and methanol and propylene glycol.

Phytochemical screening: The presence of different phytochemicals in the extract was evaluated using standard tests. The extract was dissolved in ethanol before the commencement of the tests.
Test for tannins: A 1ml quantity of ferric chloride was mixed with 1ml of the extract in a test-tube. The presence of tannins was indicated by the formation of green solution.
Test for flavonoid: A 1 ml quantity of sodium hydroxide was mixed with the extract (1 ml) in a test-tube. The presence of flavonoids was shown by formation of persistent yellow green colour.
Test for alkaloids: A 2 ml quantity of Meyer's reagent was mixed with the extract (1 ml) using a test-tube. Alkaloids presence was indicated by the appearance of yellow cream precipitate.
Test for saponins: This was done using the froth test. A 1 ml quantity of distilled water was shaken with the extract (1 ml) in a test-tube and. The presence of saponins in the extract, was shown by the formation of foam.
Test for reducing sugar: This was conducted using the Fehling's test. The appearance of brick red precipitate shows presence of reducing sugars.
Test for terpenoids: Chloroform (1 ml) was mixed with the extract (1 ml) in a test-tube. Terpenoids presence was shown by the appearance of yellow precipitate.
Test for cardiac glycosides: A 1 ml quantity of the extract was poured into a test-tube. Few drops of concentrated hydrochloric acid and 2 ml of chloroform were mixed with the extract. The presence of cardiac glycosides in the extract was shown by appearance of a red ring at the interface.

Evaluation of gels

Physical appearance: The gels were visually checked for the colour, appearance, homogeneity, phase separation and consistency.

Determination of pH: The pH of the gels was measured with a digital pH meter (HANNA instruments HI 2211 pH/ORP Meter) which was calibrated with standard buffer solutions. The measurements of pH of each formulation were done in triplicate and the mean was calculated (Baral *et al*, 2020).

Determination of viscosity: The viscosity of the gels was determined at room temperature using NJ-1 rotary viscometer with spindle no.4 at 12 rpm (Giri and Bhalke, 2019).

Determination of spreadability: Two clean slides (10 cm by 5 cm) and a 40 g weight were utilised in the evaluation of spreadability of the gels. A 0.1 g quantity of the gel was placed on the lower slide and the diameter of the circle formed by gel was measured. The second slide of known weight was placed on the slide containing the gel. The standard weight (40 g) was placed on the upper slide and was left on the slide for 60 seconds. The new diameter of the circle formed by the gel was also measured. The procedure was done in triplicate for all the gels (Chen *et al*, 2016; Pal and Chakraborty, 2020).

Homogeneity: This was done by physical evaluation by pressing a small quantity of gel between the thumb and index finger (Bolla *et al*, 2020). Homogeneity was also studied by viewing the gels under light microscope to observe the globe structure. The gel was mounted on the glass slide and observed using magnification 10X of a light microscope.

Skin irritation test: The skin irritation test was performed on the male albino Wistar rat. Standard conditions for laboratory animals (rats) were maintained. They were fed adequately with rat chow and water. The rats were shared into three groups (the control, standard and test) of five. The dorsal parts of the rats were shaven, a day before the test. During the test, the formulated gel was applied to the shaven part of the rats in the test group; to the standard group, formalin (a standard irritant) was applied and to the control group, nothing was applied. The rats were observed for any irritation (erythema or edema) (Giri and Bhalke, 2019).

Stability studies: The different gel formulations were subjected to accelerated stability studies. The formulated gels were stored in respective sealed plastic container at 40ºC for 90 days. Samples were withdrawn and analyzed every 30 days.

Anti-inflammatory studies: The anti-inflammatory studies were conducted using Wistar rats from the animal house of the Department of Pharmacology and Therapeutics, Delta State University, Abraka. Ethical approval (REC/FBMS/DELSU/ 20/82 of 16/11/2020) was obtained from the Ethical committee of the Faculty of Basic Medical Sciences, Delta State University, Abraka. The rats were left to acclimatize for a period of 10 days and were fed with normal ration of animal feed and water. A modification of the method used by Araujo *et al* (2019) was utilised in this study. Forty-five Wistar rats weighing 90 – 100 kg separated into nine groups of five were utilised in the *in vivo* anti-inflammatory study.
Group I: (Standard Group): Diclofenac gel + Carragenan (1%)
Group II: (Control Group): Carragenan (1%) alone
Group III: (Test Group 1): Formulation F1 + Carragenan (1%)
Group IV: (Test Group 2): Formulation F2 + Carragenan (1%)

Group V: (Test Group 3): Formulation F3 + Carragenan (1%)
Group VI: (Test Group 4): Formulation F4 + Carragenan (1%)
Group VII (Test Group 5): Formulation F5 + Carragenan (1%)
Group VIII (Test Group 6): Formulation F6 + Carragenan (1%)
Group IX (Test Group 7): Formulation F7 + Carragenan (1%)

A 0.1ml quantity of carrageenan (1%w/v in normal saline) was administered to the left paw of the rats in the Control, Standard and the Test groups and the time was recorded. The initial paw size was measured one (1) hour after the induction of inflammation. No further treatment was administered to the Control group. The anti-inflammatory formulation (Standard or Test gel) was applied to the inflamed paw by rubbing in the formulation fifty (50) times with the index finger on the hind paw of the animal. The readings were taken hourly to evaluate the level of paw reduction and the effect of the anti-inflammatory agent. The level of anti- inflammation on the rat paw was evaluated using the thread method. The thread was used to form a knot around the paw and at the point where the exact paw size was gotten; the thread was cut and the length measured using a meter rule in centimetre (cm). All the rats in the different groups were subjected to this process and the evaluation was done for a period of 4 hours (at hourly intervals).

The percentage value of oedema inhibition for each group was calculated using equation 2

$$\%\ Inhibition\ of\ the\ drug = \left\{1 - \frac{(y-x)}{(b-a)}\right\} X\ 100 \quad \ldots\ 2$$

Where; x = initial paw thickness of the animal in the test group; y = paw thickness of the animal in the test group after treatment; a = initial paw thickness of the animal in the control group; b = paw thickness of the animal in the control group after treatment

RESULTS

The extract is black in colour. It is partially soluble in distilled water at room temperature, but soluble in propylene glycol and warm distilled water. It is very soluble in ethanol.

Phytochemical screening: Phytochemicals present in *Dacryodes edulis* bark ethanol extract are shown in Table 2. They appear in large, small or minute quantities.

Table 2:
Phytochemicals present in ethanolic extract from *Dacryodes edulis* bark

Components	Results
Alkaloids	++
Flavanoids	+++
Tannins	+++
Saponins	+
Reducing sugars	+++
Terpenoids	++
Cardiac glycosides	+

Key: + = present in very minute quantity, ++ = present in moderate quantity, +++ = present in large quantity.

Table 3:
Physicochemical Properties of the formulated gels

Parameters	F1	F2	F3	F4	F5	F6	F7
Colour	White	White	Brown	Brown	Brown	Brown	Brown
Consistency	+++	+++	+++	++	+++	+++	+++
Phase separation	No	No	No	No	No	No	No
Homogeneity	+++	+++	+++	++	+++	+++	+++
pH	4.09	8.50	6.46	5.78	6.50	7.50	7.00
Viscosity (mPas)	14,750	14,000	>20,250	20,250	12,250	18,250	-
Spreadability (cm)	1.3	1.5	0.9	1.9	1.5	1.8	-

KEY: + = good, ++ = very good, +++ = excellent

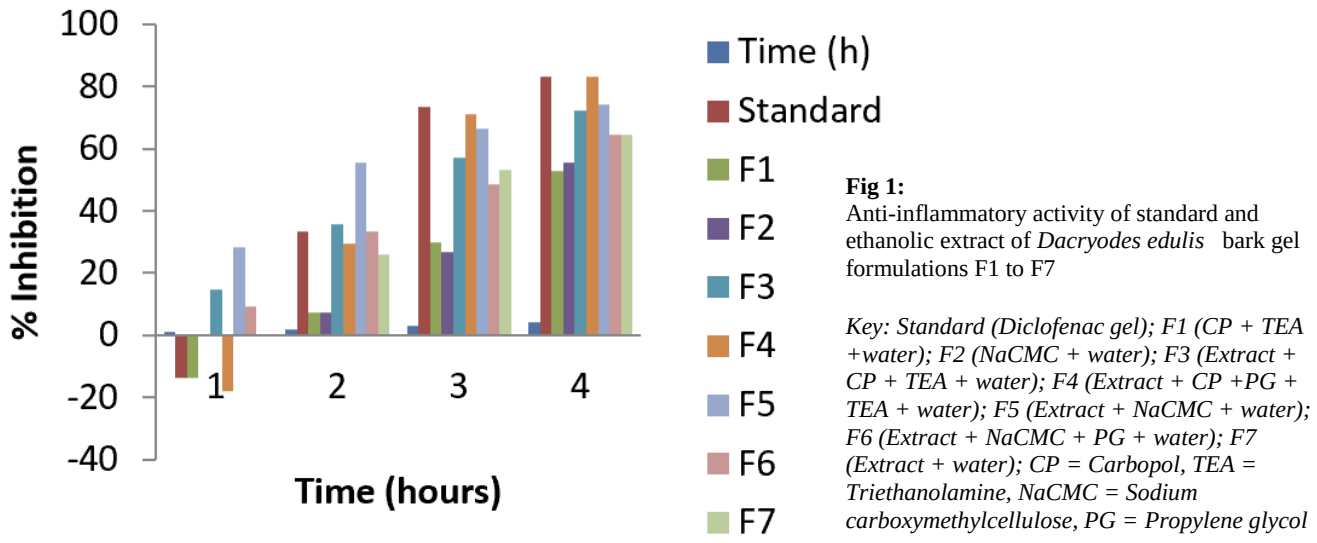

Fig 1:
Anti-inflammatory activity of standard and ethanolic extract of *Dacryodes edulis* bark gel formulations F1 to F7

Key: Standard (Diclofenac gel); F1 (CP + TEA +water); F2 (NaCMC + water); F3 (Extract + CP + TEA + water); F4 (Extract + CP +PG + TEA + water); F5 (Extract + NaCMC + water); F6 (Extract + NaCMC + PG + water); F7 (Extract + water); CP = Carbopol, TEA = Triethanolamine, NaCMC = Sodium carboxymethylcellulose, PG = Propylene glycol

Physicochemical properties: The gels that contained the extract in their formulations were brown in colour while those without the extract were white in colour (Table 3). Phase separation was not noticed in any of the formulations. They all had good homogeneity and consistency. The pH ranged from 4.1 to 8.5. Spreadability was from 0.9 to 1.9 cm. The viscosity ranged from 12,250 to greater than 20,250 mPas (Table 3)

Skin irritation study: The gels did not cause skin irritation in any of the rats used in the study.

Anti-inflammatory study: This study showed that the different gel formulations of the extract displayed anti-inflammatory activity (Fig. 1).

Stability studies: No colour change or phase separation was noticed in any of the formulations after 90 days accelerated stability study at 40oC. There was also no microbial growth.

DISCUSSION

The extract contains large quantity of flavonoids as shown by the phytochemical study and this may be responsible for the anti-inflammatory activity. Manifestation of anti-inflammatory activity by flavonoids has been reported by many researchers (Rathee *et al*, 2009; Serafini *et al*, 2010; Ginwala *et al*, 2019) and it results from the inhibition of the production and activities of several pro-inflammatory mediators like eicosanoids, adhesion molecules, cytokines and C-reactive protein (Serafini *et al*, 2010). The extract contains terpenoids in small quantity and this also contributes to its anti-inflammatory activity (Prakash, 2017). The extract contains very minute quantity of saponins which also has anti-inflammatory activity (Chindo *et al*, 2010).

The formulated gels had good physicochemical properties like good homogeneity, good consistency without any coarse particles. They had smooth texture, appealing appearance and showed no sign of phase separation.

The gels' pH was between 4.1 and 8.5 and this may explain its non-skin irritation effect (Bolla *et al*, 2020). Formulations F1, and F4 had pH values that were within the normal range of skin pH (4-6) (Ali and Yosipovitch, 2013).

The viscosity for formulation F7 was so low that no reading was recorded by spindle 4 at 12 rpm. This may be because it did not contain any gelling agent in its formulation. All the other formulations had reasonable viscosities with F3 and F4 having the highest Viscosity.

Spreadability represents the extent to which the gel spreads easily on the skin or the affected portion when applied (Durgam *et al*, 2020). The spread of gel on the skin helps to determine its therapeutic efficacy. The spreading of gel on the skin aids its uniform application therefore gels must possess good spreadability to satisfy this ideal quality in topical application. Good spreadability leads to enhanced patient compliance to treatment (Dantas *et al*, 2016). It is observed that the spreadability of a gel depends on its viscosity range (Pal and Chakraborty, 2020).

None of the gels evaluated caused skin irritation on the Wistar rats.

All the formulated gels exhibited anti-inflammatory effect, in the order F4 > F5> F3> F7 > F6 > F2 > F1. Formulation F4 exhibited the highest anti-inflammatory activity and this may be as a result of propylene glycol, a good permeation enhancer in its composition. Formulation F5's high anti-inflammatory property may also be because of the permeation enhancer. Although F1 and F2 had no active ingredient in them, they exhibited little anti-inflammatory activity which may be ascribed to the excipients in the formulations. At time T1 (one hour after the application of the formulations), it was observed that the inflammation still increased indicating that the anti-inflammation process of the gel had not started. At T3 (after three hours of administration of the formulations), the inflammation reduced, indicating that the anti-inflammatory action has commenced. This observation corresponded to that of the standard gel used. It can also be seen that F3 and F4 which contained carbopol produced higher inflammatory actions than F5 and F6 which where formulated using NaCMC. Formulation F7 that contained the extract alone exhibited anti-inflammatory activity but the effect was less than those produced by formulations with formulation enhancer (F4 and F5). The anti-inflammatory actions of F3 and F7 appeared to be similar as both formulations contained the extract but did not contain permeation enhancer. However, F3 had a slightly higher anti-inflammatory effect which may be due to the supporting excipients with individual anti-inflammatory properties. For the preparations that contained NaCMC (F2, F5 and F6), it was noticed that F5 has the greatest anti-inflammatory effect as a result of the presence of permeation enhancer. F2 exhibited the least effect due to absence of the extract.

In conclusion, *Dacryodes edulis* bark ethanolic extract has good anti-inflammatory activity. The gels formulated using the extract retained its anti-inflammatory property and formulation F4 has comparable anti-inflammatory activity to the standard gel (diclofenac gel). The gels that contained propylene glycol exhibited higher anti-inflammatory activity than those without it. The evaluated gels have good physicochemical properties such as good homogeneity, consistency, spreadability with no phase separation and did not cause skin irritation.

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