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Original Article

Synergistic Anti-Inflammatory Effect of a Polyherbal Formulation and Palm Oil on Induced Inflammatory Models in Albino Wistar Rats

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ABSTRACT

Introduction: Palm oil obtained from the mesocarp of the fruit of Elaeis guineensis is locally used to treat inflammations either alone or in combination with herbs. The present study aimed to test the basis of using palm oil (PO) as an anti-inflammatory agent and the synergistic effect of the Aqueous Extract polyherbal Formulation (AEPHF) comprising *Zingiber officinale*, *Curcuma longa,* and *Allium sativum.*

Materials and Methods: A total of 162 adult Wistar rats were used to investigate three anti-inflammatory models for eight weeks. Each model contained 54 rats (27 male and 27 female rats), with an average weight of 119 to 170 g. In the acute and sub-acute anti-inflammatory studies, 0.2 ml of carrageenan solution 1%, egg albumin, and formalin were injected subcutaneously into the paw of the rats respectively. Group 1 distilled H_2O (2 ml/kg), Group 2, 10 mg/kg of ibuprofen, Group 3, 50 mg/kg of AEPHF, Group 4, 50 mg/kg of AEPHF + 2ml/kg of PO, Group 5, 50 mg/kg of AEPHF + PO topically, Group 6, 100 mg/kg of AEPHF, Group 7, 100 mg/kg of AEPHF + 2 ml/kg of PO, Group 8, 100 mg/kg of AEPHF + PO topically, Group 9, 2 ml/kg of PO and PO topically. The diameters of the paws were recorded at intervals of 0, 0.5, 1, 2, and 3 hours (for acute inflammatory study using egg albumin and carrageenan), as well as at 0, 3, 5, and 7 days (for sub-acute inflammatory study using formalin).

Results: The results indicated that the treatment groups had significantly less paw diameter compared to the control group ($p<0.01$). Group 8, which distilled 100 mg/kg of AEPHF and PO topically, had the best effect compared to other treatment groups.

Conclusion: An increase in the dose of AEPHF revealed subsequent increases in anti-inflammatory actions. 100 mg/kg of AEPHF and PO topically proved to be the most potent in the three models of inflammations. However, further research should be carried out to determine the mechanism of action of the anti-inflammatory effect of the plant using laboratory animals.

1. Introduction

Inflammation is a key aspect of the body's immune system. It is a process in which the immune system recognizes and removes harmful and foreign stimuli and begins the healing process[1]. Inflammation occurs when tissue injury and inflammation-inducing factors, such as histamine and cytokines lead to venular dilation, increased vascular permeability, and entrance of inflammatory components. The responses to stress facilitate inflammation, which is a crucial element of the process[2].

The cardinal signs of inflammation include pain, heat, swelling, redness, and loss of function[3]. There are two types of inflammation, including acute and chronic inflammation.

Elaeis guineensis is a tropical crop belonging to the genus *Elaeis.* It is a perennial tree crop and the highest oil-producing plant in the world[4]. The fruit of this tree is a drupe that develops in proximity to one another, resulting in clusters of fruit[5]. The pericarp of the fruit comprises three cross-sectional layers, including the exocarp (skin), mesocarp (outer pulp containing palm oil), and endocarp (a hard shell enclosing the kernel that houses the endosperm). The endosperm contains oil and carbohydrates reserved for the embryo[6].

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Ginger, a tropical flowering plant native to Southeast Asia, is now widely accessible to farmers across the globe. Since ginger belongs to the Zingiberaceae family, it is closely related to turmeric[7]. The leafy plant has clusters of greenish-purple flowers and reaches a height of approximately three feet. The part of ginger used for culinary or medicinal purposes is the rhizome. The root's interior exhibits colors, such as red, yellow, or white, which vary according to the specific variety. To harvest the entire plant it is extracted from the soil, the leaves are severed, and the root is thoroughly cleaned[8].

Curcuma longa (turmeric) is a tropical plant belonging to the Zingiberaceae family. It has rhizomes which are underground stems, which may be oval, pyriform, oblong, or short-branched. Globally, especially in South Asia, including countries, such as India, China, and Pakistan, *Curcuma longa* serves as a spice, flavor enhancer, coloring agent, and preservative[9].

Allium sativum, commonly known as garlic, is a herb closely related to onion, leeks, scallion, rakkyo, and chives. Allicin is a chemical substance generated by garlic that provides its strong odour[10].

The present study aimed to compare the effect of the poly-herbal mixture of ginger (*Zingiber officinale*), turmeric (*Curcuma longa*), garlic (*Allium sativum*), and *Elaeis guineensis* oil on induced paw inflammation in Albino Wistar rats.

2. Materials and Methods

2.1. Ethical approval

The study was approved and authorized by the ethics committee of the Faculty of Life Sciences, University of Benin, with registration number LS23012.

2.2. Collecting plant sample

Disease-free samples of rhizomes of *Curcuma longa*, *Zingiber officinale,* and cloves of *Allium sativum* were purchased from the Uselu market in Egor Local Government Area in Benin, Edo State, Nigeria. A 750 ml bottle of palm oil, commonly referred to as red oil, was also purchased from the same market. The cloves and rhizomes were cut into smaller pieces and initially dried for two weeks in a shaded environment at room temperature, followed by an additional hour of drying in an electric oven set to 400 degrees Celsius. Using an electric mill, the dried cloves and rhizomes were processed into a fine powder and subsequently stored in airtight containers for future application as reported by Obaro et al.[11].

2.3. Drugs/Solvents and chemicals

The drugs, solvents, and chemicals used for the current study included Carrageenan, Formalin, egg albumin, ibuprofen, palm oil, poly-herbal extract, and distilled water.

2.4. Experimental animals

Six White albino mice comprising three males and three females aged eight weeks and weighing 25-30 g were used for the acute toxicity study.

A total of 162 adult rats aged eight weeks were used for the three anti-inflammatory models. Each model contained 54 adult Wistar rats (27 male and 27 female rats), with an average weight of 119 to 170 g. The mice and rats were purchased from the animal house of the Pharmacology/Toxicology Department in the university of Benin of the authors of the current study. The animal house of the Phytomedicine unit of the Department of Plant Biology and Biotechnology, University of Benin was kept in wooden cages at room temperature and kept in a standard laboratory environment with 12 hour cycles of light and darkness. Before the experimental study, the mice and rats were given clean water and standard pelletized layer mash to acclimatize for two weeks[11].

2.5. Experimental design

2.5.1. Acute toxicity study

An acute toxicity study was conducted using methods Obaro-Onezeyi and Obaro[12]. Six mice, including three males and three females, received 1000 mg/kg of the extract and were monitored for 72 hours for any potential toxicity, mortality, or morbidity symptoms[12].

2.5.2. Anti-inflammation studies

2.5.2.1. Acute anti-inflammation studies

The rat paw edema model was used to determine the systemic effects of the extract on acute inflammation. The experimental induction of acute edema suppression in the right paw was achieved through the injection of a 1% carrageenan solution in distilled water into the sub-plantar area of the paw, resulting in the buildup of fluid (edema) in the rat's paw, which manifested as a pronounced pink swelling. The size of the paw was assessed at various intervals using a Vernier caliper[13].

In the current study, a total of 54 adult Wistar rats, including 27 males and 27 females, aged eight weeks were used. The animals were divided into nine groups, and each group consisted of six animals.

Group 1 (Negative control) was administered 2 ml/kg distilled water, group 2 (Positive control) was administered 10 mg/kg ibuprofen, group 3 received 50 mg/kg poly-herbal extract only, group 4 received 50 mg/kg of poly-herbal extract and 2ml/kg of palm oil orally, group 5 received 50 mg/kg of extract orally and Palm oil topically, group 6 received 100mg/kg of extract only, group 7 received 100 mg/kg of extract orally beside Palm oil, group 8 received 100 mg/kg of extract and Palm oil, group 9 received 2 ml/kg of palm oil orally and 2 ml/kg of palm oil topically.

Throughout administration, rats were fed with food and water. Before induction, the dimensions of the rat's right hind paw were recorded. The third substance was administered one hour following the oral intake of the poly-herbal extract, after which 0.2 ml of a 1% solution of carrageenan/egg

albumin was injected into the sub-plantar area. The paw was measured again at various time intervals, 0 hours, 0.5 hours, 1 hour, 2 hours, and 3 hours following the injection of carrageenan. Edema was measured by assessing the increase in paw size, determined by calculating the difference in size at the initial time point of 0 hours and subsequent measurements taken at various intervals following the injection of the carrageenan/egg albumin agent. The level of edema inhibition (percentage inhibition) was calculated for each group using the following formula (where paw volume was used).

Inhibition (1%) = [1- (Vt/Vc) 100]

2.5.2.2. Chronic anti-inflammatory studies

Chronic inflammation can be identified through models that involve the repeated administration of test agents, which are utilized to assess the impact of various substances on chronic inflammation and inflammation that persists for more than 24 hours. In case the assault on the body is not contained within the acute phase, inflammation could be considered chronic. Models designed to replicate chronic inflammation of a pathological nature have been developed and employed in the evaluation of appropriate substances for its treatment. This model includes arthritis induced by formaldehyde in rats, adjuvant-induced arthritis, air pouch inflammation, collagen adjuvant-induced arthritis, and cotton pellet granuloma tests[14]. The current study used formaldehyde-induced arthritis.

2.5.2.2.1. Formaldehyde Induced Arthritis

The rat paw edema model was used to determine the chronic effects of the extract on chronic inflammation. By inhibiting the development of chronic edema, which was experimentally induced in the right paw through the injection of 0.2 ml of a 1% formaldehyde solution into the sub-plantar area of the paw. The chronic inflammatory response led to the accumulation of fluid (arthritis/edema) in the rat paw, seen as an intense pink swelling, the size of the paw was measured in terms of volume at several intervals by the means of a Vernier caliper[15].

Adult 27 males and 27 females Wistar rats aged eight weeks, were used in the present study. The animals were divided into nine groups, with each group comprising six animals.

Group 1 (Negative control) was administered 2 ml/kg distilled water, group 2 (Positive control) was administered 10 mg/kg of ibuprofen, group 3 received 50 mg/kg of poly-herbal extract only, group 4 received 50 mg/kg of poly-herbal extract and 2ml/kg of palm oil orally, group 5 received 50 mg/kg of extract orally beside palm oil topically, group 6 received extract 100mg/kg only, group 7 received extract 100 mg/kg orally and palm oil, group 8 received extract 100 mg/kg + palm oil, group 9 received 2 ml/kg of palm oil orally as well as 2 ml/kg of palm oil topically.

Throughout administration, rats were fed with food and water. Before induction, the size of the right hind paw of the rat was measured. The polyherbal extract alone or with palm oil as well as the distilled water and standard drugs were respectively administered 30 minutes after the 0.2 ml of 1% formaldehyde solution was injected into the subcutaneous region of the paws of the rats. At several time intervals, 0, 3, 5, and 7 days after formaldehyde solution injection, edema was assessed by measuring the increase in paw size. It was determined by calculating the difference in size at the initial time point of 0 hours and subsequent measurements taken at various intervals following the injection of the formaldehyde solution.

The level of inhibition (percentage inhibition) of edema was calculated for each group using the following relation (where paw volume was used):

Inhibition (1%) = [1- (Vt/Vc) 100]

2.6. Statistical analysis

Results from these experiments were provided as Mean ± Standard Error of Mean (SEM). One-way ANOVA test and Turkeys' multiple comparison tests were performed to analyze the results using GraphPad Prism 8.0 (GraphPad Software, Inc., CA, USA). ($p \leq 0.01$) used to denote the statistical significance.

3. Results

3.1. Acute Toxicity Study

The acute toxicity study showed that with a dosage of 1000 mg/kg per oral, in all treated animals, The poly-herbal extract was found to be free from any adverse side effects (Table 1). Hence the doses of anti-inflammatory studies were selected between 50 and 100 mg/kg per oral.

An acute toxicity study was carried out to determine the safety of the poly-herbal extract at a single dose of 1000 mg/kg. Obtained results revealed the LD_{50} was greater than 1000 mg/kg as there was no mortality recorded in the mice (Table 1).

3.2. Acute inflammatory test

3.2.1. Carrageenan-induced paw edema

As demonstrated in Figure 1, rats treated with five

Table 1. Acute effect of Aqueous Extract of the Polyherbal Formulation (AEPHF) on Swiss albino mice after 72 hours of administration of single-dose (1000 mg/kg)

Group(s)	Dose (mg/kg)	Cognition	Agility	Signs of toxicity, such as grooming, nausea, writhing,	Mortality after 72 hours of administration
Control	2 ml/kg	Normal	Normal	None	0/6
AEPHF	1000	Normal	Normal	None	0/6

Key: AEPHF= Aqueous Extract of the Polyherbal Formulation

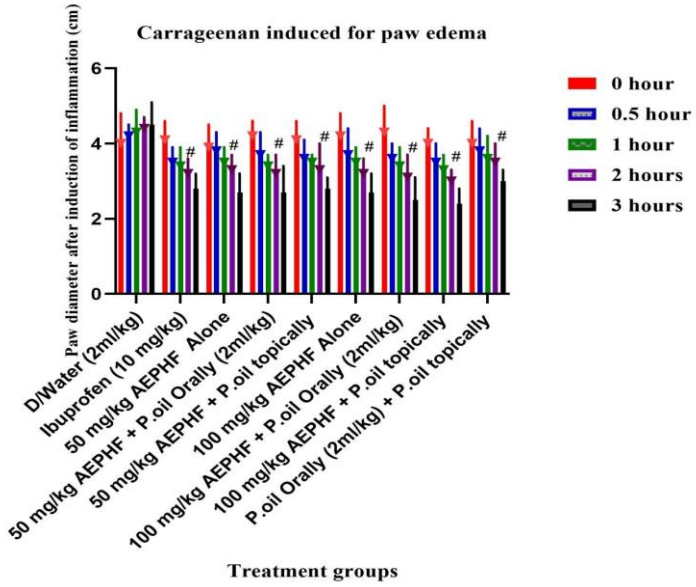

Figure 1. Effects of *Elaeis guineensis* oil and poly-herbal extract on carrageenan-induced paw edema in albino Wistar rats. (p ≤ 0.01).
Keys: AEPHF= Aqueous Extract of Polyherbal formulation;
P. oil= Palm oil

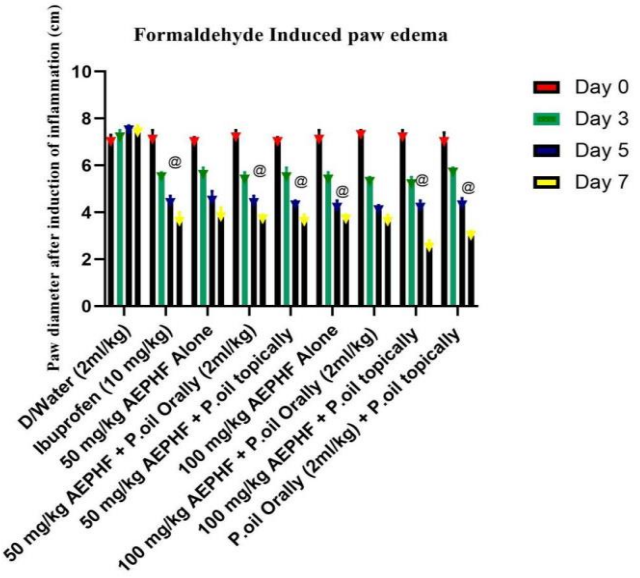

Figure 3. The effect of *Elaeis guineensis* oil and poly-herbal extract on formaldehyde-induced paw edema in albino Wistar rats. (p ≤ 0.0001).
Keys: AEPHF= Aqueous Extract of Polyherbal formulation;
P. oil= Palm oil

doses of the poly-herbal extract palm oil, and ibuprofen (10 mg/kg) exhibited a significant decrease in edema with increasing time, which were significant compared to the negative control (p ≤ 0.01).

3.2.2. Egg albumin induced paw edema

Rats treated with five doses of the poly-herbal extract palm oil, and ibuprofen (10 mg/kg) exhibited a significant decrease in edema with increasing time, which was significant in comparison with the negative control (p ≤ 0.001) (Figure 2).

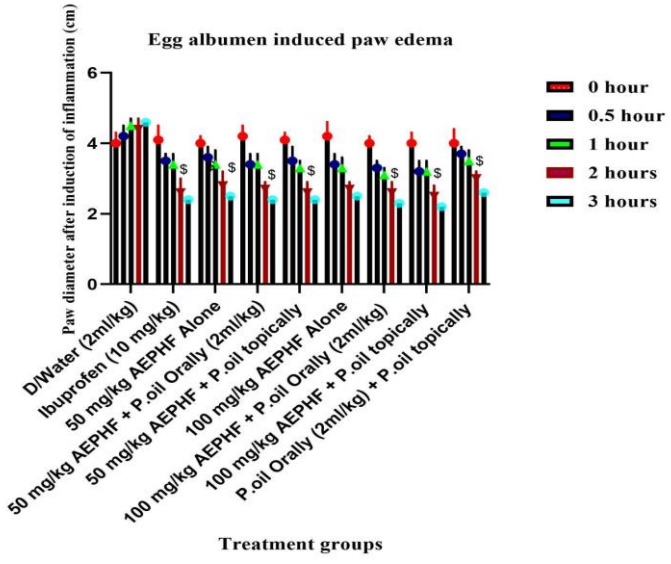

Figure 2. Effect of *Elaeis guineensis* oil and poly-herbal extract on egg albumin induced paw edema in albino Wistar rats. (p ≤ 0.001).
Keys: AEPHF= Aqueous Extract of Polyherbal formulation;
P. oil= Palm oil

3. 3. Formaldehyde induced paw edema

As can be seen in Figure 3, rats treated with five doses of the poly-herbal extract and palm oil, and ibuprofen (10 mg/kg) exhibited a significant decrease in edema with increasing time, which was significant compared to the negative control (p≤0.0001).

4. Discussion

4.1. Acute toxicity study

An acute toxicity study was carried out to determine the safety of the poly-herbal extract at a single dose of 1000 mg/kg. Results from the acute toxicity study revealed the LD_{50} was greater than 1000 mg/kg as there was no mortality recorded in the rats. This finding corroborates the finding of Obaro et al.[16].

4.2. Carrageenan induced paw edema

The induction of edema through carrageenan has been commonly employed to assess the anti-edematous properties of naturally derived products[17]. Despite having a wide spectrum of inflammatory mediators, it is commonly known that neutrophil infiltration plays a significant role in the inflammation brought on by carrageenan in the hind paw[17].

In the present study, the AEPF at doses of 50 and 100 mg/kg singly administered orally and respectively combined with palm oil orally and topically demonstrated reductions in the sizes of the paws. There was a significant difference in each treatment group compared to the standard which was composed of 10 mg/kg of ibuprofen and the negative control 2 ml/kg of

distilled water at various intervals of 0 hours, 0.5 hours, 1 hour, 2 hours and 3 hours ($p \leq 0.01$) (Figure 1). An increase in the dose of the polyherbal extract and time resulted in subsequent increases in anti-inflammatory actions in a dose-dependent manner and were noticeable in the third phase.

The combination of 100 mg/kg of polyherbal extract palm oil topically proved to be most potent with 2.4 ± 0.4 mm compared with the negative (4.5 ± 0.6 mm) and positive control (2.8 ± 0.5 mm).

The reductions in paw edema sizes corroborate the results of Mansouri et al.[17], which revealed that ellagic acid at a dosage of (5.26-14.76 mg/kg) causes a decrease in paw size in carrageenan-induced paw edema. It has been demonstrated that ellagic acid inhibits the enzymes prostaglandin-endoperoxide synthase and nitric oxide synthase, thereby preventing the release of nitric oxide and prostaglandin E2 that are in charge of producing the prostaglandin and thromboxane enzymes that cause inflammation in the body[18]. The glycosides present in the AEPF and palm oil reduce the paw size. The glycosides work by inhibiting the synthase of prostaglandins and nitric oxide from the acid of arachidonic, which is released out of the plasma membrane through phospholipases, and by blocking the activities and production of the prostaglandins and thromboxane enzymes[19].

4.3. Egg albumin induced paw edema

The anti-inflammatory efficacy of the various treatments was tested in the egg albumin-induced paw edema. Rats were subjected to an egg albumin test to induce paw edema[20].

In the present study, the AEPF at doses of 50 and 100 mg/kg singly administered orally and respectively combined with palm oil orally and topically demonstrated reductions in the sizes of paws. Each treatment group exhibited a significant difference when compared to the standard, which consisted of 10 mg/kg of ibuprofen and the negative control of 2 ml/kg of distilled water, assessed at various time intervals of 0 hours, 0.5 hours, 1 hour, 2 hours, and 3 hours ($p \leq 0.001$) (Figure 2). An increase in the dose of the polyherbal extract and time resulted in subsequent increases in anti-inflammatory actions in a dose-dependent manner noticeable in the third phase.

The combination of 100 mg/kg of polyherbal extract palm oil topically proved to be most potent with 2.2 ± 0.4 mm compared with the negative (4.6 ± 0.3 mm) and positive control (2.4 ± 0.2 mm).

The reduction in paw edema size corroborates the results of Akindele et al.[21], which evaluated *Thuja occidentalis* hydroethanolic leaf extract with a dosage of 50, 100, 200, and 400 mg/kg for a period of 0.5, 1, 1.5, 2, 2.5, 3 hours. It was indicated that statistically substantial inhibitory activity on the growth of rat paw edema in the egg albumen-induced test, with the anti-inflammatory action being the most noticeable in the third phase. The results imply that the polyherbal extract and palm oil hindered the secretion and activities of vasoactive compounds, such as kinins, serotonin, histamine, as well as prostaglandins. Given that the discharge of prostaglandin-like substances is linked to the late stage of albumin of egg-induced edema, it is suggested that the impact of secretion and activity prostaglandins is highly associated[22] and is comparable to clinically effective anti-inflammatory drugs, such as the steroidal and non-steroidal drugs[23]. This supports one of the mechanisms through which the extract demonstrates its noted anti-inflammatory effects: The suppression of histamine and serotonin secretion activities[24].

4.4. Formaldehyde induced paw edema

The main purpose of formaldehyde test is to determine the ability of a drug to neutralize inflammatory responses. Formalin irritates the skin which results in pain and localized inflammatory reaction. Since injection of formalin causes edema and increased vascular permeability, rats were used in the study's formaldehyde test to stimulate paw edema[22].

In the current study, the AEPF at doses of 50 and 100 mg/kg singly administered orally and respectively combined with palm oil orally and topically demonstrated reductions in the size of paws. As Figure 3 demonstrates, there was a significant difference in each treatment group compared to the standard which was composed of 10 mg/kg of ibuprofen and the negative control 2 ml/kg of distilled water at various intervals of day 0, day 3, day 5 and day 7 ($p \leq 0.0001$). An increase in the dose of the polyherbal extract and days resulted in subsequent increases in anti-inflammatory actions in a dose-dependent manner noticeable on day 7.

The combination of 100 mg/kg of polyherbal extract palm oil topically proved to be the most potent with 2.5 ± 0.3 mm compared with the negative (7.4 ± 0.5 mm), and positive control (3.6 ± 0.4 mm).

The obtained results in the formaldehyde test revealed that the polyherbal extract significantly impedes the effect on inflammation. Inhibiting the activities of enzymes arachidonic acid to prostaglandins and thromboxane is crucial in controlling physiological systems, including inflammatory and immune reactions. The findings corroborate with the work of Obaro et al.[25]. Prostaglandins are small potent inflammatory mediators that are created by the secretion of arachidonic acid from the membrane phospholipids by the phospholipase A2 family[26], thus resulting in a decrease in the paw size through reduction of the vascular permeability which is similar to the ibuprofen (10 mg/kg) inhibition of inflammation[27].

5. Conclusion

The present study demonstrated the acute toxicity and the effect of the aqueous extract of a polyherbal formulation comprising *Zingiber officinale*, *Curcuma longa,* and *Allium sativum* as anti-inflammatory agents as well as

the synergistic use of palm oil. The acute toxicity study revealed that the poly-herbal extract had an LD_{50} greater than 1000 mg/kg as there was no mortality recorded in the mice; hence the doses of anti-inflammatory studies were selected between 50 and 100 mg/kg per oral. The AEPF at doses of 50 and 100 mg/kg singly administered orally and respectively combined with palm oil orally and topically demonstrated reductions in the sizes of paws. An increase in the dose of the polyherbal extract revealed subsequent increases in anti-inflammatory actions in a dose-dependent manner noticeable at the third phase and day 7. The combination of 100 mg/kg of polyherbal extract palm oil topically proved to be most potent the carrageenan, egg albumin, and formalin-induced inflammations. However, further research should be carried out to determine its mechanism of action.

Declarations

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors affirm their involvement in the paper as follows: Examine development and planning: Dr. Obaro P. O.. Data collection, analysis, and interpretation of results: Dr. Obaro P. O. Dr. (Mrs.) Obaro-Onezeyi O.E. and Dike M.A. Draft manuscript and preparation: Dr. Obaro P. O. Dr. (Mrs.) Obaro-Onezeyi O.E. and Dike M.A. The final draft of the manuscript was approved by the authors after they had evaluated.

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Availability of data and materials

The manuscript contains all datasets generated and/or analyzed in the current study.

Ethical considerations

The authors have examined the work for plagiarism, data falsification, multiple publications, and redundancy. The ethics committee of the Faculty of Life Sciences, University of Benin, with registration number LS23012, also authorized the study.

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