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Anti-inflammatory activities of aqueous and ethanolic extracts of *Lophira lanceolata*'s Van Tiegh. ex Keay (Ochnaceae) leaves

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Abstract
The WHO Benin 2021 report clearly indicates that hepatitis B and C kill as much, or more than HIV/AIDS or malaria in Benin. Liver diseases are characterized by inflammation, and in Benin, the leaves of the *Lophira lanceolata* Van Tiegh. Ex Keay plant are extensively utilized for treating such conditions. This study aims to demonstrate the anti-inflammatory properties of *Lophira lanceolata* leaves. To conduct the study, ethanolic and aqueous extracts of *Lophira lanceolata* leaves were prepared using traditional methods and the leaves themselves. Larval toxicity and acute oral toxicity tests indicate that both the aqueous and ethanolic extracts of *Lophira lanceolata* leaves are non-toxic. At doses of 500 and 1000 mg/kg body weight, both extracts significantly reduced paw edema induced by carrageenan in Wistar rats. At 1000 mg/kg body weight, both extracts alleviated tail pain caused by water at 50 °C. Furthermore, both the aqueous and ethanolic extracts diminished Brewer's yeast-induced hyperthermia in Wistar rats. Phytochemical screening of the extracts unveiled the presence of alkaloids, polyphenols, flavonoids, tannins, saponosides, anthocyanins, free anthracene derivatives, leuco-anthocyanins, quinone derivatives, and reducing compounds. These components may be responsible for the observed pharmacological properties.

Keywords: *Lophira lanceolata*, anti-oedematous, antipyretic, analgesic

Introduction
Inflammation serves as a manifestation of various diseases, including those affecting the liver [1-3]. Despite its essential role in the survival of an organism under attack, inflammation is not without harm [4]. In Benin, as in many other countries, viral hepatitis poses a significant public health challenge. According to the World Health Organization (WHO), hepatitis B and C contribute to mortality rates comparable to or even surpassing those of HIV/AIDS or malaria in Benin [5]. Liver diseases are inherently inflammatory.
The widespread prescription of non-steroidal anti-inflammatory drugs (NSAIDs) and steroidal anti-inflammatory drugs (SAIDs) underscores their efficacy in managing pain, fever, inflammation, and rheumatic disorders. However, their prolonged use often comes with side effects such as gastrointestinal ulcers and renal failure [6,7]. Exploring medicinal plants has emerged as an important alternative to discover drugs with fewer adverse effects [8]. WHO reports indicate that 80% of the population already embraces traditional medicine [9], drawn by its deep-rooted cultural significance and accessibility for treating diseases through herbal remedies [10].
Lophira lanceolata, a species of the Ochnaceae family, thrives in dry savannah woodland areas and is widespread in Central and West African countries like Senegal, Cameroon, Sudan, and Ivory Coast [11]. It is also found in Benin, where its leaves are employed in treating various ailments, including hypertension, diarrhea, and diabetes [12,13,14,15]. Surveys among traditional practitioners have revealed that the leaves of *Lophira lanceolata are* hepatoprotective (anti-inflammatory) but no scientific evidence is available to justify these pharmacological properties of the plant. It is in this context that we proposed to conduct this study to provide scientific evidence for the anti-inflammatory utilization of this plant in traditional medicine.

Materials and Methods
Materials

Plant material
We gathered *Lophira lanceolata* leaves from the Pahou forest and had them authenticated at the National Herbarium of the University of Abomey-Calavi, where they were assigned the registration number AAC 231/HNB. After drying under laboratory conditions, they were reduced to powder and stored in a dark, dry place.

Animal material
The animal model chosen was female Wistar rats weighing between 120 and 150g. We obtained them from the Animal House of the Human Biology Unit of the Faculty of Health Sciences. The temperature in the animal house was 25°C, with alternating light and dark periods of 12 hours each. The rats have free access to water and food. We carried out the *in vivo* tests on the rats in accordance with current OECD guidelines, in order to comply with ethical guidelines on experimental pain in conscious animals [16].

Chemical and pharmaceutical products
Ethanol 96°, carrageenan, indomethacin 100 mg, Aspegic 50 mg, brewer's yeast (*Saccharomyces cerevisiae*) [Arkopharma] were used in the present study.

Methods
Preparation of extracts
Both aqueous and ethanolic extracts were prepared by decoction at 10% for 30 minutes and maceration at 10% under mechanical agitation for 72 hours. After filtration on whatman paper and reduced-pressure evaporation at 50°C on a rotary evaporator (Büchi Rotavapor 200), the decoction and concentrated macerate were oven-dried to obtain the dry extracts, which were scraped off and stored in the refrigerator.

Anti-oedematous activity
The investigation into the anti-oedematous properties followed the methodology outlined in reference [17]. Wistar rats, weighing between 120 and 150 g, were categorized into six groups (N = 7). The control group received physiological water, while the remaining groups were administered ethanolic and aqueous extracts of *Lophira lanceolata* leaves (at doses of 500 mg/kg and 1000 mg) and indomethacin (100 mg/kg). Edema was induced by injecting 1% carrageenan (NaCl : 0.9%) beneath the plantar aponeurosis of the right hind paw of the Wistar rats.
Paw volume measurements were taken prior to carrageenan injection and at 1, 2, 3, 4, 5, and 6 hours post-injection. The mean edema volume in the treated paw was determined based on three measurements. The assessment of anti-oedematous activity involved calculating the percentage increase and reduction in edema in treated rats compared to the control group using the following formulas :
The volume of edema (Vt) at a specific time point (t_i) is :

The percentage increase A in foot volume is given by :

$A=100\ Vt/\ V_o$

[$Vt = Vt_i - V_o$, V_o : Initial foot volume; Vt_i : Foot volume at time t_i]

The percentage of P-inhibition of edema is given by:
$P = 100(Vt_f - Vt_p)/\ Vt_f$ [Vt_f : Volume of edema in control rats; Vt_p : Volume of edema in treated rats]

Analgesic/antalgic activity
The analgesic effect of the extracts is investigated in animals by the "Tail flick" method. We divided the Wistar rats weighing between 120 and 150 g into six lots (N = 7). The control group was given physiological water, while the other groups were orally administered ethanolic and aqueous extracts of *Lophira lanceolata* leaves (at doses of 500 mg/kg and 1000 mg/kg) and Aspegic at 50 mg/kg. The administration of *Lophira lanceolata* leaves extracts and Aspegic was conducted orally. One hour after the product administration, each rat's tail was immersed in hot water maintained at 50°C. The time taken by the rat to withdraw its tail was recorded as the reaction time [18]. Lysine acetylsalicylate (Aspegic) at 50 mg/kg was used as a reference product.

Antipyretic activity
After obtaining rectal temperatures from rats grouped into six sets (N = 7), each animal received intraperitoneal 20% brewer's yeast at a dose of 1 mL/kg body weight [19]. Subsequently, the animals underwent a fasting period. Seventeen hours later, control rectal temperatures were measured for all rats [20,21]. The installation of hyperthermia being obtained after 17 hours, the different lots received per os, the ethanolic and aqueous extracts of *Lophira lanceoalta* leaves and Aspegic. One hour after oral product administration, temperatures were recorded every hour for six hours [18,22]. The control group received physiological water, while the remaining groups were given ethanolic and aqueous extracts of *Lophira lanceolata* leaves (at doses of 500 mg/kg and 1000 mg/kg) and lysine acetylsalicylate (Aspegic) at 50 mg/kg, serving as a reference product.

Acute oral toxicity test
Acute oral toxicity was performed on two batches of rats (N = 6), each of which received a single dose of 2000 mg/kg body weight, of each of the extracts of *Lophira lanceolata* leaves. On the first day, these rats were placed under observation for four (4) hours and then each day for the remaining thirteen (13) days.

Phytochemical screening
The identification of the primary chemical compound groups present in both aqueous and ethanolic extracts was conducted utilizing the [23] method. This method relies on distinctive staining and precipitation reactions.

Statistical analysis
Statistical analysis was conducted utilizing the Excel 2013 spreadsheet, and the comparison of measurements means between batches was carried out through Student's t-test ($p < 0.05$).

Results and Discussion
The evolution of edema, the percentage of edema increase, and the percentage of edema inhibition are given by Figures 1, 2, 3. Tail dwell time and rectal temperatures are given by Figures 4 and 5.
The initial volume of the foot of the Wistar rats was not identical in the different batches.
In the control lot, edema volume increased from 0.00 cm^3 at time t_0 to 0.38±0.05 (63.33±0.87%) and 0.57±0.07 cm3 (95.00±1.18) at time 1 and 6 hours after carrageenan injection, respectively (Figure 1 & 2). Edema volume at the Extaq 1000 and Exteth 1000 lots increased from 0 to 2 hours

before initially decreasing. But in the Indo 100, Extaq 500 and Exteth 500 batches, this volume started to decrease after 3 hours after carrageenan injection (Figure 2).

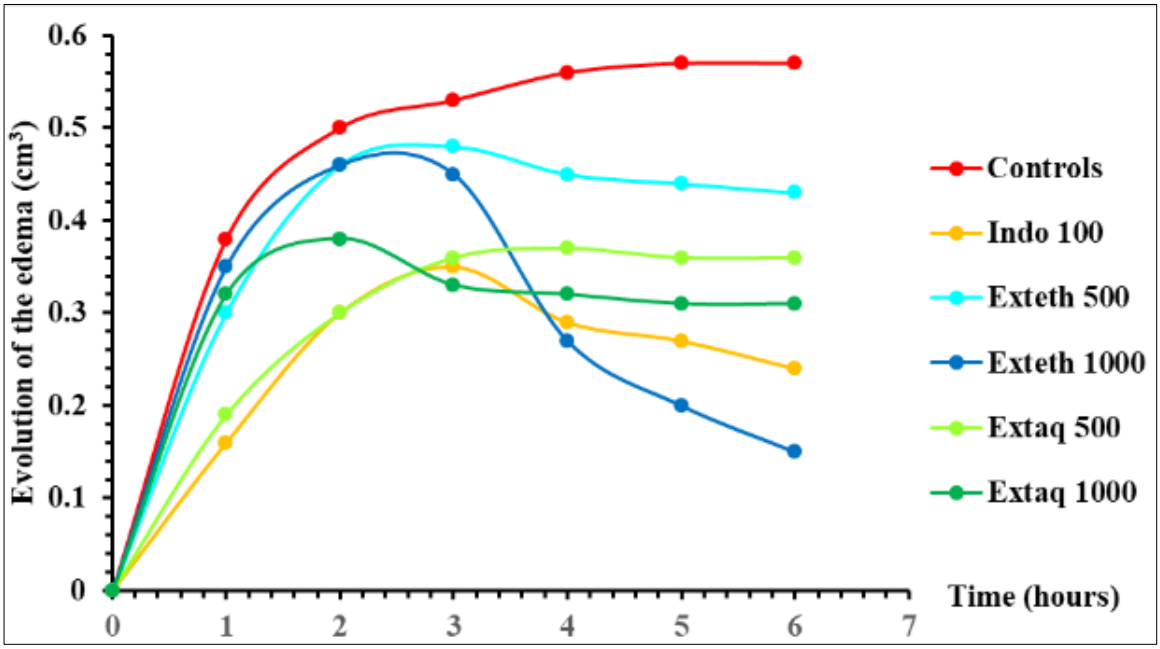

Fig 1: Evolution of right paw edema in Wistar rats during anti-oedematous activity. N = 7 per group. Values are mean±mean standard errors obtained with Excel 2013, $p< 0.05$, compared with control group (Student's t test). Ethext: Ethanolic extract of *Lophira lanceolata* leaves, Aqext: Aqueous extract of *Lophira lanceolata* leaves.

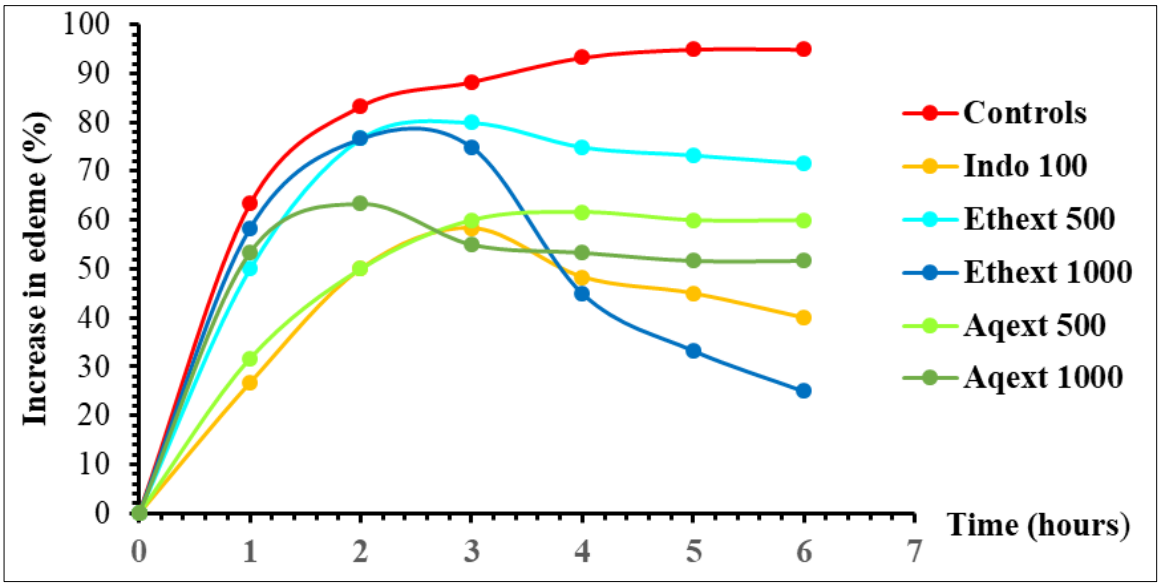

Fig 2: Percentage increase in right paw edema of wistar rats during anti-oedematous activity. N = 7 per group. Values are mean±mean standard errors obtained with Excel 2013, $p< 0.05$, compared with control group (Student's t test). Ethext: Ethanolic extract of *Lophira lanceolata* leaves, Aqext: Aqueous extract of *Lophira lanceolata* leaves.

Leaf extracts of *L. lanceolata* are administered 30 minutes before carrageenan injection. The results are illustrated in Figure 3.

The different doses of *L. lanceolata* leaf extracts significantly inhibited carrageenan-induced edema ($p < 0.05$). After 1 hour, the strong inhibition was recorded with indometacin 100 (57.89±0.35; $p < 0.05$) and Extaq 500 (50.00±0.90; $p < 0.05$) but indometacin was more effective. After 2 hours, indomethacin and Extaq 500 inhibited in virtually the same way, their percent inhibition being 40.00±1.47%; $p < 0.05$ and 40.00±1.70%; $p < 0.05$, respectively. It was after 4 hours that Extaq 1000, Exteth 500 and Exteth 1000 had strong inhibition with their respective inhibition percentages of (42.85±1.07; $p< 0.05$); (19.64±1.76%; $p< 0.05$) and (51.78±1.01%; $p< 0.05$). The highest inhibition was recorded after 6 hours with their respective percentages of (45.61±0.77%; $p< 0.05$); (24.56±1.34%; $p< 0.05$) and (73.68±0.97%; $p< 0.05$).

Before 4 hours, indomethacin (reference product) was more effective than all extracts. However, after 4 hours, it was only more effective than Exteth 1000, the percentages of inhibition of indomethacin and Exteth 1000 being respectively after 6 hours of (57.89±0.91; $p< 0.05$); (73.68±0.97%; $p< 0.05$). The degree of inhibition is then dose and time dependent and also dependent on the type of extract.

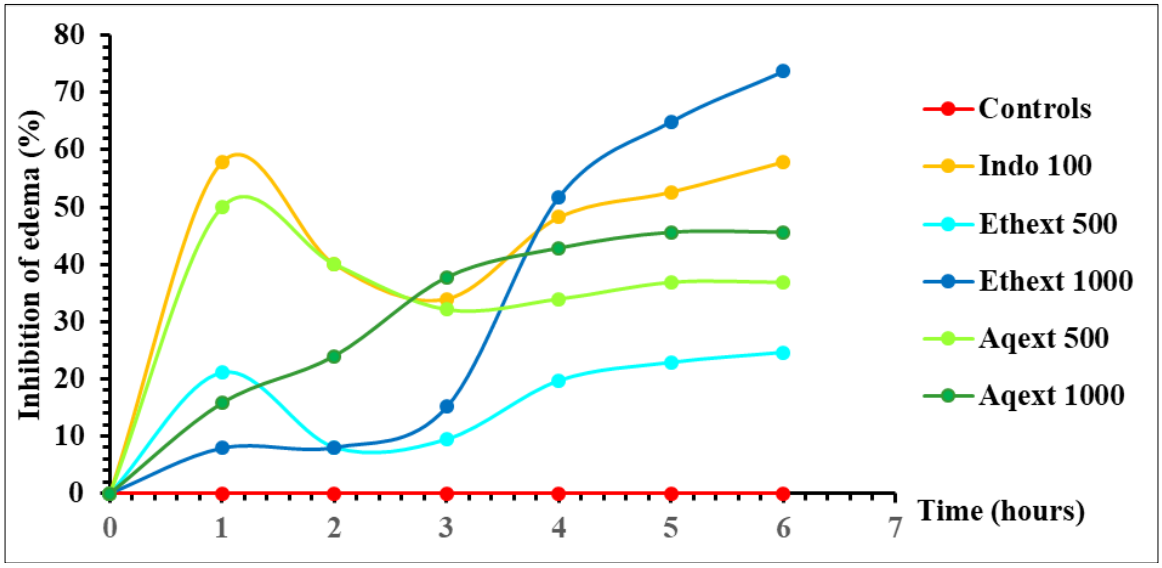

Fig 3: Percentage inhibition of right paw edema in wistar rats during anti-oedematous activity. N = 7 per group. Values are mean±mean standard errors obtained with Excel 2013, $p< 0.05$, compared with control group (Student's t test). Ethext: Ethanolic extract of *Lophira lanceolata* leaves, Aqext: Aqueous extract of *Lophira lanceolata* leaves.

Figures 1, 2 and 3 show the effect of indomethacin, ethanolic and aqueous extracts of *Lophira lanceolata* leaves as a function of time one the edema induced by carrageenan in the paw of the Wistar rat (N = 7). After the injection of 1% carrageenan to the right hind paw, the volume of the edema of the control rats increased exponentially from 0.38±0.005 cm^3 after 1 hour to 0.57 cm^3 after 6 hours or a percentage increase in edema after 1 hour from 63.33±0.87% to 95±1.18% after 6 hours. On the other hand, that of the legs of the Indo 100, ethext500, ethext1000, aqext500, aqext1000 lots increased significantly after 1 hour from 0.16±0.005 cm^3; 0.3±0.01 cm^3; 0.35±0.006 cm^3; 0.19±0.006 cm^3; 0.32±0.008 cm^3 respectively to 0.24±0.010 cm^3, P < 0,05; 0.43±0.006 cm^3, P < 0,05; 0.15±0.009 cm^3, P < 0,05; 0.36±0.008 cm^3, P < 0,05; 0.31±0.003 cm^3, $p< 0,05$ after 6 hours or a percentage increase in edema after 1 hour of 26.66±0.86%; 50±1.75%; 58.33±1.15%; 31.66±1%; 53.33±1.49% to 40±1.82%, $p< 0,05$; 71.66±1.08%, $p< 0,05$; 23.97±1.60%, $p< 0,05$; 60±1.45%, $p< 0,05$; 51.66±0.66%, $p< 0,05$ after 6 hours. Except for the controls where the evolution and the percentage of increase reflect an exponential curve, for the other lots, the evolution and the percentage reach their maxima before going down significantly after 6 hours. Thus the maxima are observed after 2 hours in the lots ethext1000 (0.46±0.004 cm ^{3}- 76.66±0.79 %, $p< 0.05$) and aqext1000 (0.38±0.009 cm^3 - 63.33±1.61%), after 3 hours in the Indo 100 (0.35±0.00 cm^3 - 58.33±1.09 %, $p< 0.05$) and ethext500 (0.48±0.007 cm^3 - 80±1.32%, $p< 0.05$) and after 4 hours in the aqext500 lot (0.37±0.004 cm^3 - 61.66±0.74%, $p< 0.05$). The less important evolution and percentage increase are recorded with the Indo 100 lot compared to the other lots except after 4 hours where the exteth1000 lot seems to have the lower evolution and percentage increase than the indo 100. The progression and the percentage of increase validate the inhibitory effects exerted by both ethanolic and aqueous extracts of *Lophira lanceolata* leaves. Between the two doses of 500 mg/kg and 1000 mg/kg of body weight, the 1000 mg/kg dose appears to be more potent, with the ethanolic extract demonstrating over 70% inhibition (73.68±0.97%, $p< 0.05$) of carrageenan-induced paw edema in rats after 6 hours. In contrast, the aqueous extract exhibits inhibition of nearly 50% (45.61±0.77%, $p< 0.05$) during the same period. The ethanolic extract proves to be more effective than the aqueous extract and even surpasses the effectiveness of indomethacin (57.89±0.91%, $p< 0.05$). Both the ethanolic and aqueous extracts of *Lophira lanceolata* leaves demonstrate significant effects on rat paw edema induced by carrageenan, a potent phlogistic agent [24]. The effects of these extracts (500 mg/kg and 1000 mg/kg b.w.) are comparable to those of indomethacin at 100 mg/kg b.w., highlighting their natural anti-inflammatory properties. Notably, the ethanolic extract at 1000 mg/kg b.w. exhibits significantly stronger anti-inflammatory properties than indomethacin. Carrageenan injection-induced edema serves as a widely adopted animal model for assessing the anti-inflammatory activity of substances. This inflammatory response involves the release of various chemical mediators, with carrageenan activating cyclo-oxygenase [25]. The biphasic nature of the inflammatory response includes an initial phase (0-2.5 hours post-injection) attributed to mediators like histamine, serotonin, and bradykinin affecting vascular permeability, and a delayed phase characterized by prostaglandin overproduction mediated by cyclo-oxygenase (COX) and extending beyond 5 hours post-injection [26, 27, 28]. Ethanolic and aqueous extracts of *Lophira lanceolata* leaves exhibit dose-dependent inhibition of edema across all phases. This suggests that these extracts may contain compounds with anti-histaminic, anti-bradykinic, and anti-serotonic properties, inhibiting prostaglandin biosynthesis. Notably, strong edema inhibition is observed after 5 hours for both doses of ethanolic extracts and the aqueous extract at 1000 mg/kg b.w., and within the first hour for the aqueous extract at 500 mg/kg b.w. This implies that the inhibitory action of the ethanolic extracts (500 mg/kg and 1000 mg/kg b.w.) and the aqueous extract at 1000 mg/kg b.w. of *Lophira lanceolata* leaves is primarily directed towards cyclo-oxygenases responsible for prostaglandin synthesis. In contrast, the inhibitory action of the aqueous extract at 500 mg/kg b.w. opposes the release of histamine, serotonin, and bradykinin. Indomethacin, used as a reference product, demonstrates a potent inhibitory action on the release of these mediators and on cyclo-oxygenases responsible for prostaglandin synthesis.

Figure 4 shows the analgesic/antalgic effect of ethanolic and aqueous extracts of *Lophira lanceolata* leaves by the "Tail flick" test

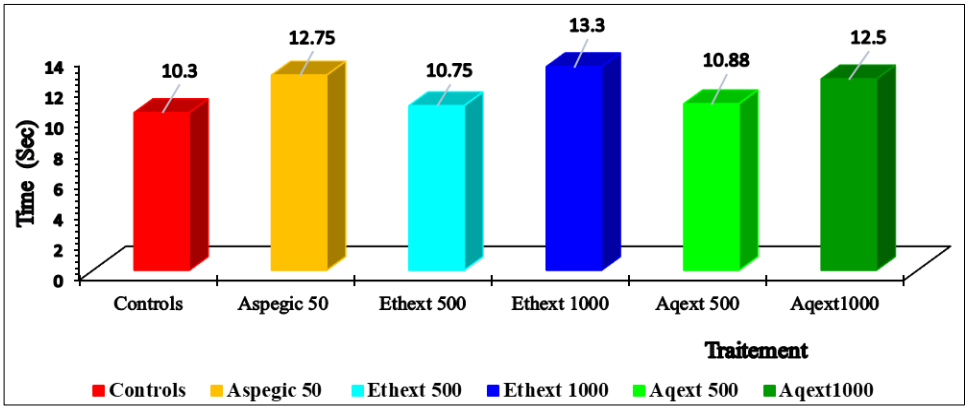

Fig 4: Tail dwell time of rats in water. N = 7 per group. Values are mean±mean standard errors obtained with Excel 2013, P < 0.05, compared to control group (Student's t test). Ethext: Ethanolic extract of *Lophira lanceolata* leaves, Aqext: Aqueous extract of *Lophira lanceolata* leaves.

Tail dwell time in water at 50°C was greater if the animals were protected. Ethanolic extract of *L. lanceolata* at 1000 mg/kg gives a longer stay (13.3±1.25 s) compared to Aspegic (reference product) at 50 mg/kg (12.75±0.40 s), ethanolic extract at 500 mg/kg (10.75±1.08 s), aqueous extract at 1000 mg/kg (12.50±0.75 s), aqueous extract at 500 mg/kg (10.88±1.26 s) (Figure 4). But this time is not significantly different from that of Aspegic at 50 mg/kg. Comparing both aqueous and ethanolic extracts at the same dose, there is no significant difference but it is significant for different doses. The difference is also significant when comparing the reference product with the two extracts at the dose of 500 mg/kg.

Administration of *L. lophira* extracts to the animals showed that these aqueous and ethanolic extracts at 1000 mg/kg and Aspegic at 50 mg/kg increased the tail dwell time of the animals in water maintained at 50°C to 12.50±0.75 s; 13.3±1.25 s and 12.75±0.40 s, respectively, compared to the unprotected controls whose tails dwelled for only 10.3±0.85 s. This time was not significantly different from those of the aqueous and ethanolic extracts at 500 mg/kg, which were 10.88±1.26 s (p> 0.05) and 10.75±1.08 s (p> 0.05) respectively. These results show that *L. lophira* extracts at 1000 mg/kg have a similar effect to Aspegic at 50 mg/kg. They thus have a clear analgesic/analgesic effect which would be dose-dependent. These extracts would have inhibited the mechanical and chemical precursors of pain thanks to the polyphenolic compounds, in particular the flavonoids which are endowed with analgesic properties [29, 30, 31]. In fact, nociceptive nerve endings are rhythmically excited by the variation of arteriolar pressure from a mechanical point of view and are chemically excited by histamine, bradykinin and prostaglandins. The painful impulses of inflammation can be explained by this pressure variation [32, 33]. The extracts would therefore exert an action that would prevent compression (excitation) of nerve endings. These results prove that the aqueous and ethanolic extracts of *L. lanceolata* at the dose of 1000 mg/kg are effective painkillers when administered 1 h in advance.

Figure 5 shows the antipyretic effect of ethanolic and aqueous extracts of *Lophira lanceolata* leaves on hyperthermia induced by the injection of a brewer's yeast solution (20%).

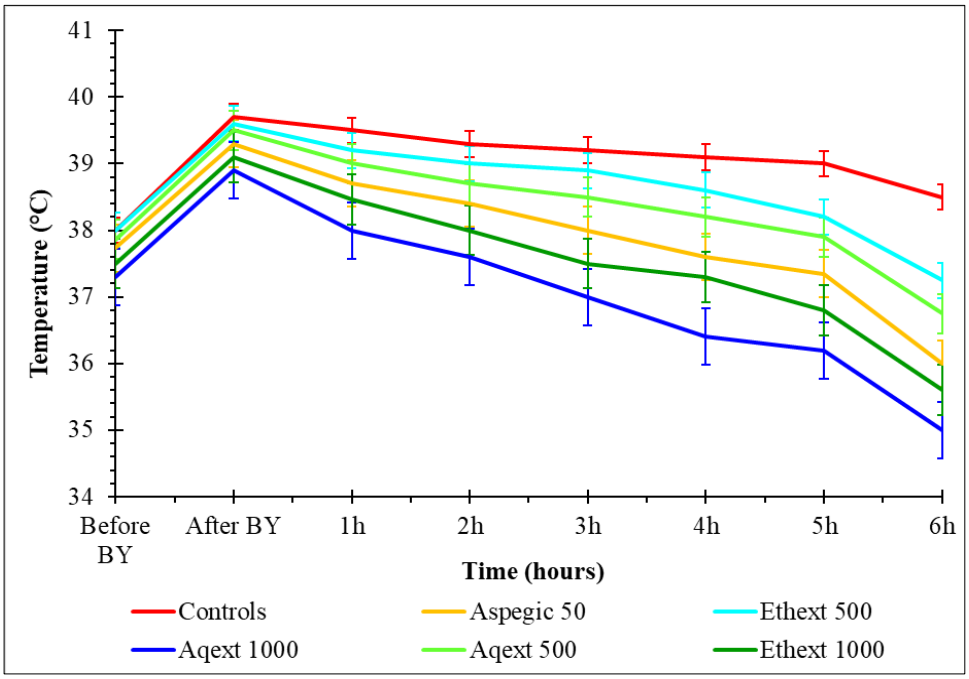

Fig 5: Evolution of rectal temperatures. N = 7 per group. Values are mean±mean standard errors obtained with Excel 2013, P < 0.05, compared to control group (Student's t test). L.l. ethext: Ethanolic extract of *Lophira lanceolata* leaves, L.l. aqext: Aqueous extract of *Lophira lanceolata* leaves. BY : Brewer's yeast

Before induction of hyperthermia by brewer's yeast, the initial temperature in the controls group was 38.00±0.46 °C. It rose to 39.70±0.67 °C 24 h after induction, and then began to drop progressively until it reached 39.70±0.67 °C. It increases to 39.70±0.67 °C 24 h after induction, and then begins to drop progressively to 38.50±0.85 °C after 6 h. Analysis of Figure 5 shows that only the ethanolic extract of *L. lanceolata* at 1000 mg/kg significantly decreases the temperature (P = 0.001). The temperature decreased from 39.1±0.35 °C to 38.46±1.29 °C after 1 h and then to 35.6±1.07 °C at the 6th hour. It was more effective than Aspegic 50 mg/kg during the 6 h of the experiment. Aspegic 50 mg/kg and both extracts at 500 and 1000 mg/kg significantly decreased the temperature during all 6 h.

From the analysis of the curves (Figure 5), it can be said that ethanolic extract of *L. lanceolata* leaves at the dose of 1000 mg/kg caused a significant reduction in hyperthermia (P = 0.001) at the sixth hour. Aspegic at 50 mg/kg, ethanolic extract at 500 mg/kg, and aqueous extract at 500 and 1000 mg/kg also reduced hyperthermia ($p< 0.05$) at the 6th hour. The induced hyperthermia resulted in the release of cytokines (TNFα, IL 1β, IL6) that activate prostaglandin (PGE) biosynthesis after reaching the blood vessels in the vicinity of the thermoregulatory hypothalamic center [34, 35]. The antipyretic effect of these extracts could be due to the reduction of cytokine release and prostaglandin biosynthesis. The ethanolic extract at 1000 mg/kg would be the most effective and its inhibitory effect is comparable to other plant species such as *Eucalyptus citriodora* [18], *Cissus quadrangularis* [20] which manages to significantly lower the temperature in 1h.

Acute oral toxicity test

Following oral administration of 2000 mg/kg body weight of ethanolic and aqueous extracts of *Lophira lanceolata* leaves, rats were observed individually for eight (8) hours on the first day and during the 14 days. No death was recorded during the experimental period. The rats did not show any symptoms of toxicity (change in behavior, respiration, food and water consumption, hair loss etc.). However, a considerable increase in body weight is observed. Indeed, Wistar rats increased by 30±5 g two weeks after oral administration of the extracts while controls increased by 20±2 g. Therefore, both extracts appear to be non-toxic up to a dose of 2000 mg/kg body weight, so the lethal dose for rats should be greater than 2000 mg/kg body weight.

Phytochemical screening

Table 1 displays the categories of chemical compounds found in the ethanolic and aqueous extracts of *Lophira lanceolata* leaves.

Table 1: Chemical groups of *Lophira lanceolata* leaves extracts

Chemical groups	Aqueous extract	Ethanolic extract
Saponosides	+	+
Alkaloids	+	+
Polyphenols	+	+
Flavonoids	+	+
Tannins	+	+
Triterpenoids	-	-
Steroids	-	-
Cardenolides	-	-
Quinone derivatives	+	+
Anthocyanins	+	+
Leuco-anthocyanins	+	+
Reducing compounds	+	+
Anthracene derivatives	-	-
Mucilage compounds	+	-
Cyanogenic derivatives	-	-

+ = Presence - = Absence

The phytochemical screening of *Lophira lanceolata* leaves extracts revealed the presence of alkaloids, flavonoids, tannins, polyphenols, saponosides, anthocyanins, quinone derivatives, reducing compounds, and leuco-anthocyanins, as indicated in Table 1. In a related study, [15] reported similar chemical groups in the aqueous extract of *Lophira lanceolata* leaves, with a few exceptions such as reducing compounds and mucilage compounds. Additionally, catechic tannins, gallic tannins, steroids, and C-heterosides were identified in their findings. The discrepancies between the two sets of results may be attributed to variations in the geographical location and harvesting period of the plant. The enhanced efficacy of both ethanolic and aqueous extracts of *Lophira lanceolata* leaves can be attributed to the specific chemical compound groups present, particularly the abundance of polyphenolic compounds. Notably, these extracts contain flavonoids known for their ability to inhibit oxidants released by leukocytes and other phagocytes within the inflammatory zone, thereby regulating inflammation [36, 37, 38, 39, 40, 41, 42, 43].

Conclusion

The investigation into the anti-inflammatory activity of aqueous and ethanolic extracts from *Lophira lanceolata leaves*, conducted on Wistar rats through tests evaluating anti-oedematous, analgesic/antalgic, and antipyretic activities, revealed notable effects at various doses. Both extracts demonstrated anti-oedematous, analgesic, and antipyretic effects on the rats under study. The anti-inflammatory attributes of these extracts can be linked to the presence of various chemical groups, including alkaloids, flavonoids, tannins, polyphenols, saponosides, anthocyanins, quinone derivatives, reducing compounds, and leuco-anthocyanins. These findings provide a rationale for the traditional use of *Lophira lanceolata* leaves in African traditional medicine for managing inflammatory processes.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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