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Research Article

Antioxidant, Anti-Inflammatory and Wound Healing Activities of *Cochlospermum planchonii* Hook. F.

Nakpane Fankibe[1], Yendubé T. Kantati[1]*, Kossi Metowogo[1], Bignoate Kombate[1], Kojdo Adi[1], Kossitsè Itiblitse[1], Tchin Darré[2], Kwashie Eklu-Gadegbeku[1] and Kodjo A. Aklikokou[1]

[1] Physiopathology, Bioactive Substances and Innocuity Research Unit (PBSI). Laboratory of Physiology / Pharmacology. Faculty of Sciences, University of Lomé – TOGO. 01BP 1515

[2] Department of Anatomy and Cytopathology, Sylvanus Olympio University Hospital Center, Lomé, Togo

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*Address for Correspondence:

Yendubé T. Kantati, PhD, Assistant Professor, Physiopathology, Bioactive Substances and Innocuity Research Unit (PBSI). Laboratory of Physiology / Pharmacology. Faculty of Sciences, University of Lomé – TOGO. 01BP 1515
ORCID ID: https://orcid.org/0000-0002-7515-494X

Abstract

Objective: The medicinal plant *Cochlospermum planchonii* Hook.f. is used in the management of various ailments in Togolese pharmacopoeia. In this study, we aimed to evaluate the antioxidant and anti-inflammatory activities of roots and leaves of *C. planchonii*, and burn wound healing activity of its leaf hydroethanolic extracts in rodents.

Materials and Methods: Antioxidant activities were assessed using Phosphomolybdenum assay, 2,2-diphenyl-1-picrylhydrazyl (DPPH) test and the reducing power assay. Visceral pain model, formaldehyde-induced paw edema and vascular permeability test were performed to evaluate anti-inflammatory activities *in vivo*. Burns were induced in rats by applying on the skin of the dorsal region an aluminum plaque preheated to 100°C for 10 seconds. Animals were treated topically with empty Carbopol gel, *C. planchonii* leaves extract 2.5 and 5 % in Carbopol gel, and Brulex® (Zinc oxide 15 % cream).

Results: *C. planchonii* extracts exhibited good antioxidant capacities close to standard compound, ascorbic acid. Leaves and root hydroethanolic extracts (1000 mg/kg), compared to control animals, significantly reduced the number of writhings ($P<0.001$) and the volume of paw edema ($P<0.001$). Similarly, both roots and leaf extracts at 1000 mg/kg have significantly inhibited vascular permeability by approximately 50% compared to the control group. *C. planchonii* leaves hydroethanolic extract 2.5 and 5 % in Carbopol enhanced wound healing via significantly increased contraction rates (78.63 ± 1.57 and 79.68 ± 1.48 respectively on day 12, $P<0.001$), confirmed by histological observations.

Conclusion: *C. planchonii* can promote burn healing due to anti-inflammatory, antioxidant and antimicrobial properties of the plant.

Keywords: *Cochlospermum planchonii*, inflammatory, antioxidant, edema, burn wound

INTRODUCTION

During the twentieth century, remarkable studies in synthetic organic chemistry have been conducted, leading to the production of synthetic drugs. Despite this progress, natural products and mimic of natural product remains the principal source of around 65% of all new approved drugs[1]. The medicinal plant *Cochlospermum planchonii* belongs to the Bixaceae family. Its roots are used in West African pharmacopoeia to treat several diseases, including gonorrhea, jaundice, burns, snake bites, malaria, palpitations, fever, diarrhea and dysentery[2]. Because infections are often cited among the causes of delayed healing and especially death due to burn wounds, we previously studied the antimicrobial activity of this plant root and leaves extract against four pathogenic bacteria frequently isolated from wounds[3]. However, the anti-inflammatory and antioxidant activities of roots extracts of *C. planchonii* harvested in Togo, two main pharmacological properties that could also explain its burn healing activity remain unexplored. In fact, wound healing involves four programmed phases, namely hemostasis, inflammation, proliferation, and remodeling[4,5]. Convergent data on cicatrization also show that a delayed inflammatory phase may lead to free radical production, which, due to their damaging effects on cells and tissue, are noxious to the wound healing process[6,7]. It became necessary to investigate the anti-inflammatory and antioxidant activities of roots extracts of *C. planchonii* used in traditional medicine in Togo. Furthermore, the utilization of roots could affect the plant survival. In accord with the biodiversity preservation statements, we considered that it was necessary to investigate the burn wound healing potential of *C. planchonii* leaves in this study. The objectives of this study are then to evaluate the antioxidant and anti-inflammatory activities of roots and leaf hydroethanolic extracts of *C. planchonii* on one hand, and the burn wound healing activity of the leaves of this plant on the other hand.

MATERIALS AND METHODS

Chemical

Formaldehyde, acetic acid and 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) were provided by Sigma Chemicals (St. Louis, USA). Indomethacin was purchased from Troge Medical GmbH (Hamburg, Germany). All other chemicals and reagents used were of the analytical grade.

Plant material and extraction

Plant material

Organs (roots and leaves) of *C. planchonii* were harvested in Kabou (TOGO) in the month of September 2018. A voucher specimen was identified and deposited in the herbarium of the Laboratory of Botany and Plant Ecology under the number Togo15501.

Preparation of the hydroethanolic extracts

Roots and leaves of *C. planchonii* collected were protected from light during drying under air conditioning in the Laboratory of Physiology/Pharmacology, Faculty of Sciences, University of Lomé (Togo). The dried roots and leaves of *C. planchonii* were ground to powder and 300 g of each was macerated in 4 litres of ethanol-water mix (5:5.v/v) for 72 hours, as described previously[3] (Fankibe *et al.*, 2020). The filtrate was then evaporated under vacuum at 40°C using a rotavapor (Buchi R- 210)[8]. The extraction yields were calculated following equation:

Yield (%) = (W1 × 100) /W2

In this formula, W1 is the weight of the extract residue obtained after evaporation and W2 is the weight of dried roots or leaf powder used.

In vitro Antioxidants Assays

Total Antioxidant Capacity

The phosphomolybdenum method[9] of Amezouar *et al*. (2013) was used to access the total antioxidant capacity of the extracts. A 0.3 mL of extract was combined with 3 mL of reagent solution (0.6 M sulfuric acid, 28 mM sodium phosphate and 4 mM ammonium molybdate). The tubes containing the reaction solution were incubated at 95°C for 90 min. Then, the absorbance of the solution was measured at 695 nm using a UV-VIS spectrophotometer (Genesys 20, Thermo Scientific) against blank after cooling to room temperature. Methanol (0.3 mL) in the place of extract was used as the blank. The total antioxidant activity is expressed as the number of gram equivalents of ascorbic acid. The calibration curve was prepared by mixing ascorbic (0, 25, 50, 100, 150, 200 and 250 µg/mL) with methanol.

DPPH antioxidant Assay

We used for this test the method[10] of Sen *et al*. (2010). A volume (1.5 mL) of different concentrations of the extract diluted in methanol was mixed with 0.5 mL of the methanol solution of DPPH (0.1 mM). An equal amount of methanol and DPPH without sample was served as a control. After 30 min of reaction at room temperature in the dark, the absorbance was measured at 517 nm against methanol as a blank using a UV-VIS spectrophotometer (Genesys 20, Thermo Scientific). Concentrations of the antioxidant required to inhibit the initial coloration of DPPH by half, IC50s of ascorbic acid, root extract (RE) and leaf extract (LE), were determined.

Reducing power assay

According to the method described by Ferreira *et al*. (2007), volumes of 2.5 mL of different concentrations of the extracts (25, 50, 100, 200 and 400 µg/mL) were mixed with 2.5 mL phosphate buffer solution (0.2 M, pH = 6.6) and 2.5 mL of 1% potassium ferriccyanide [$K_3Fe(CN)_6$] in test tubes[11]. The mixtures were placed in a water bath at 50°C, for 20 min. 2.5 mL of 10% trichloroacetic acid was added to the mixtures and mixed thoroughly. A volume of 2.5 mL of these mixtures was then added to 2.5 mL of distilled water and 0.5 mL of FeCl3 (0.1% solution) and allowed to stand for 10 min. Finally, the absorbance of this mixture was measured at 700 nm using a UV-VIS spectrophotometer (Genesys 20, Thermo Scientific). The higher the absorbance of the reaction mixture, the greater the reducing power. Ascorbic acid was used as a positive control. All these procedures were done in triplicate.

In vivo protocols

Animals

For these experiments, females ICR mice (25-35 g) and Wistar rats (200-280 g) were used. Animals were raised in the animal house of the Faculty of Science of the University of Lomé, housed in standard polypropylene cages and maintained under standard laboratory conditions (temperature 24-25 °C, relative humidity and a 12t/12 h light-dark cycle). They had free access to food and water. Institutional guidelines and ethical principles of Physiology/Pharmacology laboratory (University of Lome-Togo, ref: 001/2012/ CB-FDS-UL) were followed.

Study of acute anti-inflammatory activities *in vivo*

Acetic acid writhing test

For the visceral pain model[12], 3 % acetic acid was injected intraperitoneally sixty minutes after mice (six groups, n = 6) received orally 0.9 % NaCl (negative control), roots and leaves hydroethanolic extracts 500 and 1000 mg/kg bw (RE 500, RE 1000, LE 500, LE 1000), Indomethacin 500 mg/kg (positive control group). The results are expressed as the number of contortions observed during the 20 min period following acetic acid injection.

Formalin-induced edema test

Thirty minutes after extracts administration, edema was induced on the right hind paw of the rat by a subplantar injection of 0.1 mL of formalin (2.5 %). Rats (six groups, n = 6) received orally 0.9 % NaCl (negative control), roots and leaf hydroethanolic extracts 500 and 1000 mg/kg bw (RE 500, RE 1000, LE 500, LE 1000), Indomethacin 500 mg/kg bw (positive control group). The volume of rat paw was measured in all groups after treatments following a well-established method[13,14]. Inserting the inflamed paw in a tube of fluid elevates the fluid level (volumes), and test and control levels can be compared. Measurements were performed at 1, 3, 6, 12, 24 and 48 hours after the injection of formalin.

Vascular permeability assays

Using a previously described protocol[15], mice were divided in four groups (n = 6) and treated orally with 0.9 % NaCl (negative control), roots and leaves hydroethanolic extracts 1000 mg/kg bw (RE 1000, LE 1000), Indomethacin 500 mg/kg bw (positive control group). One hour after treatment, under anesthesia induced using the open mask method with diethyl ether, the mice received an intravenous injection of Evans blue dye (1 %) and inflammation was induced immediately after by intraperitoneal injection of a 0.7 % acetic acid solution. Thirty minutes after the injection of acetic acid, the mice were sacrificed by cervical dislocation. After five mL of saline was injected into the abdominal cavity, the washings were collected into test tubes and then centrifuged at 2000 rpm for 10 min. The absorbance of the supernatant was read at 630 nm against a saline blank using a UV-VIS spectrophotometer (Genesys 20, Thermo Scientific).

The percentage inhibition of vascular permeability was determined by the following formula:

PI (%) = [(ACG – ATG) / ACG] × 100

Where PI is Inhibition Percentage, ACG is the Absorbance of the control group and ATG is the absorbance of the treated groups.

Burns wound healing effects of *C. planchonii* leaves hydroethanolic extract

Gels preparation

Carbopol gels were prepared following steps described below: 0.3 g of Carbopol 974P NF (Goodrich, USA) was dispersed in 27 g of distilled water and mixed by stirring continuously on a magnetic stirrer (IKA-Combimag RCT) at 800 rpm for 1 h. The mixture under continuous stirring was neutralized by drop-wise addition of NaOH 1 mol/L. Mixing was continued until a transparent gel was formed. Three types of gel formulations were prepared: empty gel, gel containing 2.5 % and 5 % of *C. planchonii* leaves extract. For standard treatment we used dermal Brulex® (Zinc oxide 15 % cream) as a reference drug.

Burn Wound Induction

Animals were anesthetized with diethyl ether by the open mask method. Their dorsal surfaces were shaved by using a shaving machine. A deep second degree burn wound was induced by applying an aluminum plaque (Rayon: 3.5 mm) preheated to 100°C within boiling water, on the depilated dorsum of rat skin for 10 seconds with an equal weight and pressure[16,17]. Immediately after the procedure of burn wound induction, the burned animals were randomly divided into four groups of 8 rats and treated topically with empty Carbopol gel (Gel control), *C. planchonii* leaves hydroethanolic extract 2.5 and 5 % mixed in Carbopol gel, or Brulex® (Zinc oxide 15 % cream) in the positive control group. After topical application of creams, the wound was covered with the sterile plain gauze for 24 hours. The treatments were applied topically once a day, starting from the wound induction until day 12 post-excision.

Measurement of wound area

The images of the wounds were taken every day using the same instrument (Sony DSC-HX60V Digital Camera) and settings, fixed distance of the camera from the wound and the same position of rats. Then the photos were analysed, and the wound area of each animal was evaluated on days 3, 6, 9 and 12 post-surgery using the ImageJ 1.48v freeware [(National Institutes of Health, USA; https://imagej.nih.gov/ij), 2774K, 640MB, < 1%][18,19]. The healing rates (Tx) were calculated from the wound surface values using an equation:

$$Tx\ (\%) = [(A0 - At)/A0] \times 100$$

where A0 is the original wound area, and at is the area of wounds on days 3, 6, 9 and 12 post-surgeries.

Histological Studies

On day 6, three (3) rats from each group were sacrificed by cervical dislocation and wounds were collected for histological analysis. On day 12, the remaining rats in all groups were sacrificed by cervical dislocation for histological analysis. The biopsies planned for the histological tests were stored in 10% formalin. Skin wound samples were fixed in 10% neutral buffered formalin, processed and included in paraffin. Five-micrometer skin sections were cut and stained with haematoxylin-eosin (H&E). The tissues were qualitatively assessed under light microscopy (Olympus BX 51) at 200x magnification. Epithelialization, necrosis, fibroblast proliferation, inflammatory cells, hair follicles and neovascularization were analyzed.

Statistical analysis

Data are expressed as percentages and mean ± SEM. Analysis of variance (ANOVA One way) followed by the Bonferroni test was used to compare groups. GraphPad Prism 6.05 software was used. Values were considered significant when $P< 0.05$.

RESULTS

Extraction yields

The yields of 27.21 % for root extract (RE) and 16.25 % for leaf extract (LE) were obtained.

Antioxidant activities of *C. planchonii* leaves and root hydroethanolic extracts

Total anti-oxidant capacity and DPPH scavenging activities

Table 1 summarizes data obtained from phosphomolybdenum and DPPH assays. In comparison with root extracts (RE), leaves extracts (LE) had the lowest total antioxidant capacity (TAC) expressed as the number of gram equivalents of ascorbic acid (reference compound). Similarly, leaf extracts (LE) exhibited the highest inhibition concentrations (IC50) against DPPH free radicals, showing therefore, that the reduction capacity of root extracts is greater than that of leaf extracts. IC50 value found for ascorbic acid, the reference compound, was 20.3 ± 0.73 µg/mL.

Table 1: Total anti-oxidant capacity (TAC) and IC50 of *C. planchonii* leaves and root hydroethanolic extracts

		C. planchonii	
	Ascorbic acid	RE	LE
TAC (µg AAE/mg)	-	268.23 ± 0.59	222.09 ± 0.78
IC50 (µg/mL)	20.3 ± 0.73	42.47 ± 1.28	59.21 ± 1.86

Values are Mean ± SEM (n=3). TAC = Total antioxidant capacity assessed using phosphomolybdenum, AAE= ascorbic acid equivalent, IC50 = Concentration of the extract or the reference compound required to inhibit the initial coloration of DPPH by half. RE= Roots Extract, LE = Leaves Extract.

Ferric Reducing Antioxidant Potential

Test results show that *C planchonii* roots and leaf hydroethanolic extracts have a reducing capacity closer to that of ascorbic acid (Figure 1). It is also noted that root extracts have a higher ferric reduction capacity than leaf extracts.

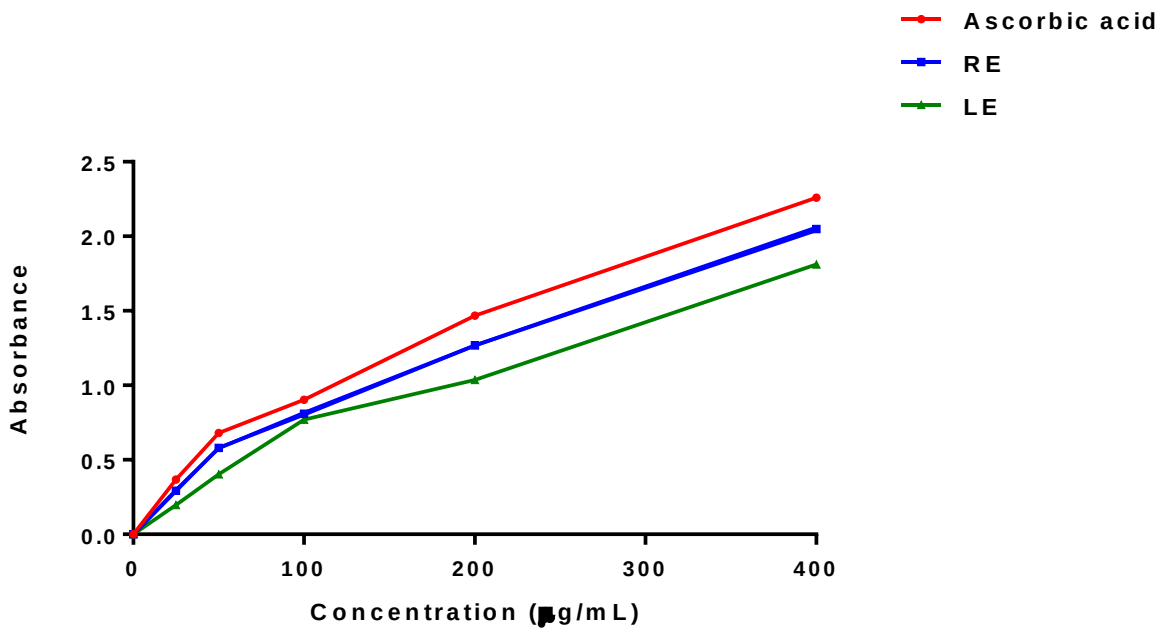

Figure 1: Evolution of absorbance with concentrations showing the reducing potential of ascorbic acid and hydroethanolic extracts.

The reducing potential of ascorbic acid and the extracts was assessed using the Fe3+/ferricyanide complex reduction method. Values are Mean ± SEM (n=3). RE= Roots Extract, LE = Leaves Extract

Anti-inflammatory activities *in vivo*

Writhing test

The anti-inflammatory activities of *C. planchonii* leaves and root hydroethanolic extracts, as determined using the acetic acid-induced contortions test, are shown in Figure 2. Both leaves (LE) and roots (RE) hydroethanolic extracts (500 and 1000 mg/kg) promoted a statistically significant reduction in the level of writhing compared to the control group. A statistically similar result was found with standard Indomethacin 500 mg/kg.

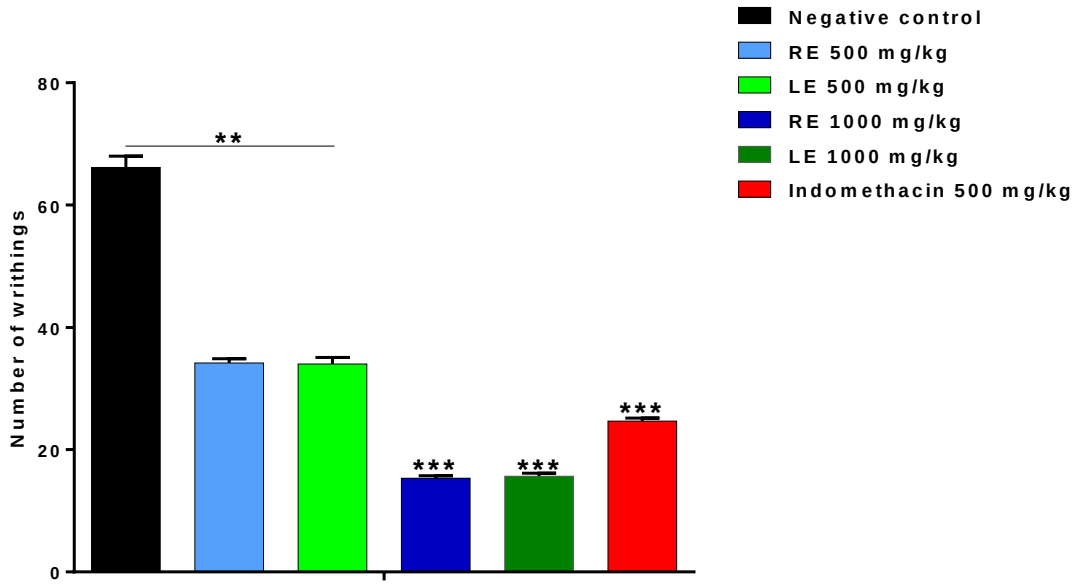

Figure 2: Number of writhings induced by acetic acid in mice treated or not with

Data are expressed as mean ± SEM. **p < 0.01 and ***p < 0.001, compared with the negative control group; n = 6. RE= Roots Extract, LE = Leaves Extract.

Formalin Induced Edema Test

The results shown in Figure 3 indicate that animals that received orally *C. planchonii* leaves and root hydroethanolic extracts significantly inhibited formalin-induced edema in comparison to the negative control group, particularly 6 hours after the injection of formalin (P<0.001).

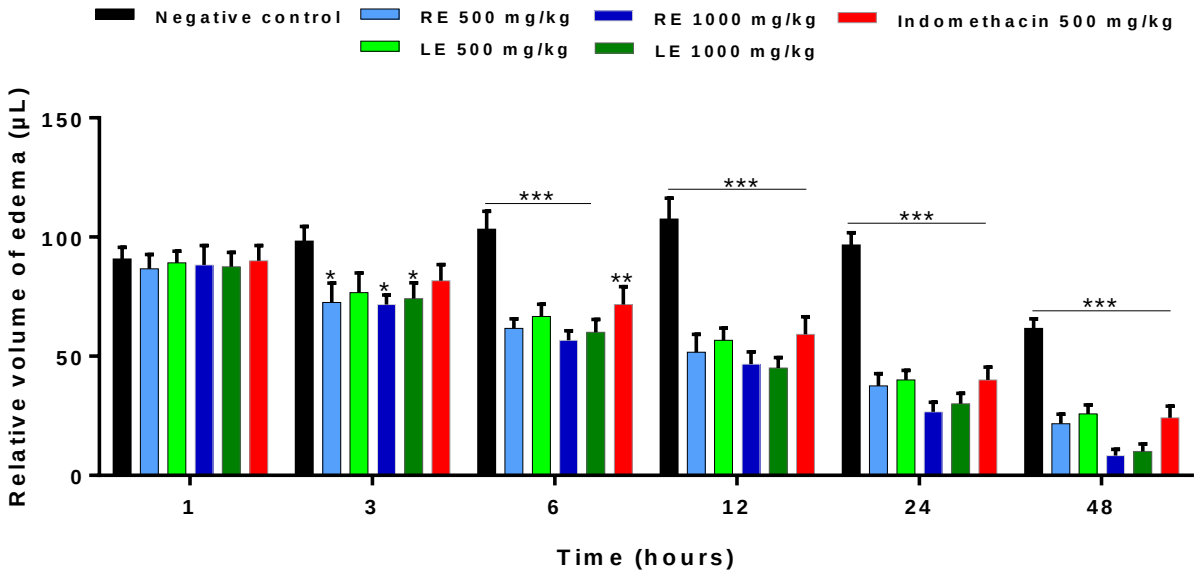

Figure 3: Effect of *C. planchonii* and indomethacin on the volume of edema induced by a formalin injection in rats.

The relative volume of the paw (fluid level) was measured at different times after intraplantar injection of formalin. Results are represented as mean ± SEM. *p < 0.05, **p < 0.01 and ***p < 0.001, compared with the negative control group; n = 6. RE= Roots Extract, LE = Leaves Extract.

Acetic Acid-Induced Vascular Permeability

Vascular permeability induced chemically (such as seen with acetic acid) caused an immediate, sustained reaction as shown in negative control (Figure 4) which was significantly inhibited by *C. planchonii* roots and leaf extracts (1000mg/kg, P<0.001).

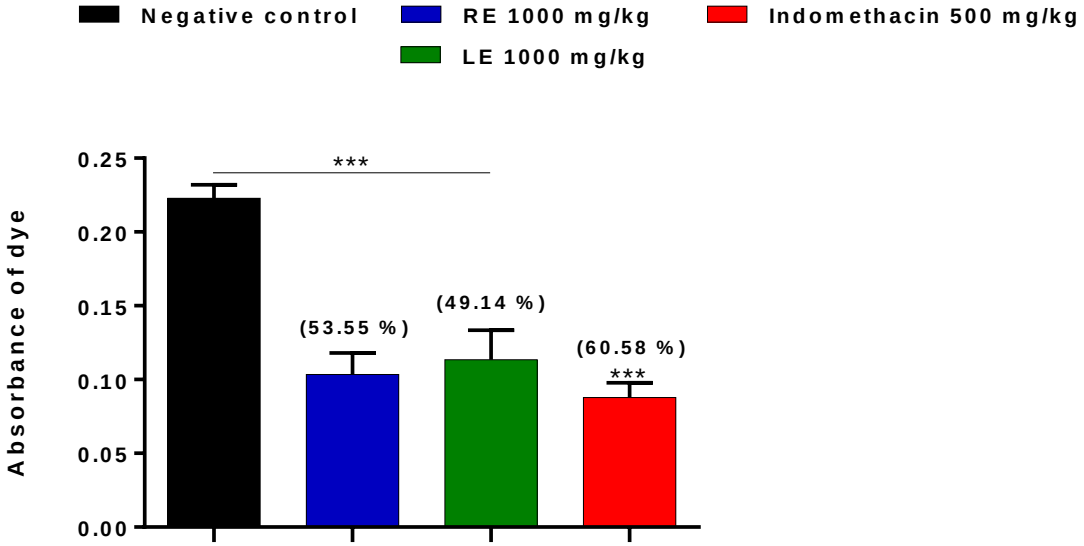

Figure 4: Effects of *C. planchonii* and indomethacin in the acetic acid induced vascular permeability.

Values are expressed as means ± SEM. ***p< 0.001, compared to the control group, n = 6. (%) represents percentage inhibition of dye leakage into peritoneum cavity. RE= Roots Extract, LE = Leaves Extract.

Burn wound healing activities of *C. planchonii* leaf extract

Wound area

Significant differences were found when comparing wound areas of groups on third day post-burn injury. *C. planchonii* 2.5 and 5 % gel groups exhibited lower wound size compared to Gel control group ($p<0.01$). There were not any significant differences between *C. planchonii* 2.5 and 5 % gel groups and the reference cream (Figure 5).

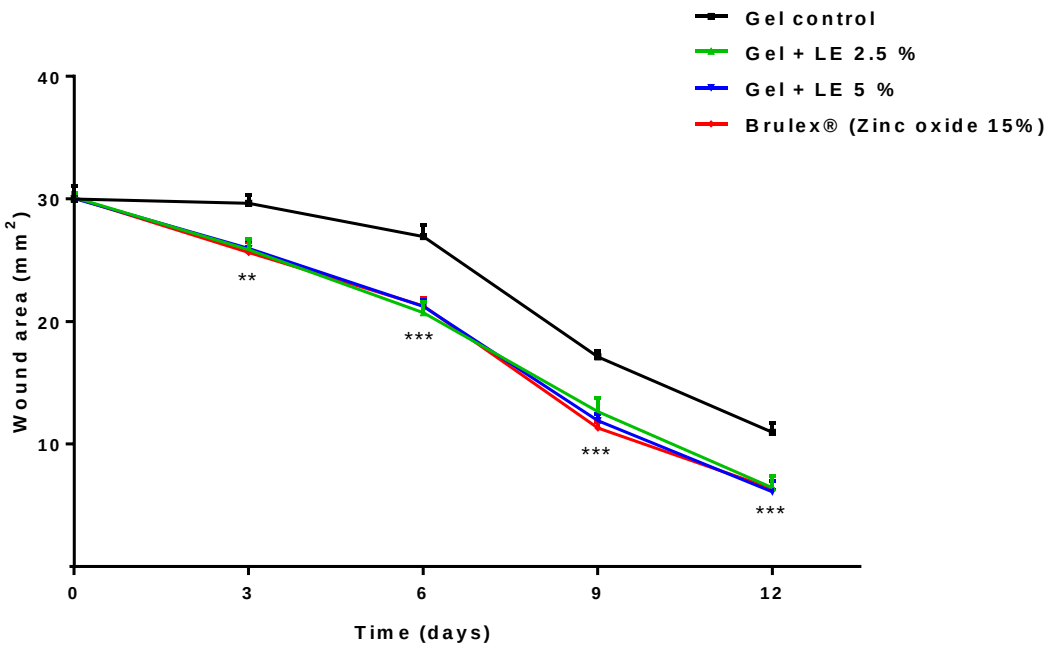

Figure 5: Wound area (mm^2) of the animal groups treated with topical ointments

Values are expressed as means ± SEM. **p< 0.01 and ***p< 0.001, compared to the Gel control group, n = 8. LE = Leaves Extract.

Wound contraction rates

Table 2 presents the calculated values of the closure progression of the wounds in different Groups with time. After application of *C. planchonii* leaves extract 2.5 and 5 % topically onto burned wounds, the area of wounds reduced respectively 14.16 and 13.58 % of their original size on day 3, 31.21 and 29.34 % on day 6, 78.63 and 79.68 % on day 12 (Table 2). The wound contraction rates in animals treated with reference drug, Brulex®, were similar to those of animals treated with *C. planchonii* leaves extract 2.5 and 5 % (14.79 % on day 3, $P<0.01$).

Table 2: Percentage of wound contraction in *C. planchonii* treated rats and Gel control groups

Wound contraction (%)				
Days	**Gel control**	**Gel + LE 2.5 %**	**Gel + LE 5 %**	**Brulex®**
J0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
J3	1.13 ± 0.88	14.16 ± 1.24**	13.58 ± 0.97**	14.79 ± 1.18**
J6	10.22 ± 1.25	31.21 ± 1.18***	29.34 ± 0.66***	29.30 ± 0.92***
J9	42.98 ± 0.88	57.99 ± 1.88***	60.37 ± 0.84***	62.43 ± 0.83***
J12	63.48 ± 1.25	78.63 ± 1.57***	79.68 ± 1.48***	78.89 ± 0.98***

Values are expressed as means ± SEM. **p< 0.01 and ***p< 0.001, compared to the Gel control group, n = 8. LE = Leaves Extract.

Histological examinations

Figure 6 represents H&E-stained wound sections on days 6 and 12 post-wounding. On day 6, re-epithelization was initiated gradually from the wound margin toward the wound center in rats treated with *C. planchonii* leaf extract and Brulex®. In Gel control group, the re-epithelization was not initiated, and the presence of necrosis was observed. Moreover, no hair follicles were observed, but there was an abundance of inflammatory cells in these animals (Table 3). On day 12, the epithelial layer was completely formed in rats receiving *C. planchonii* leaf extract and Brulex®. At this time point, hair follicle formation in rats treated with *C. planchonii* leaf extract and Brulex® was significantly higher than those of the Gel control group (Table 4).

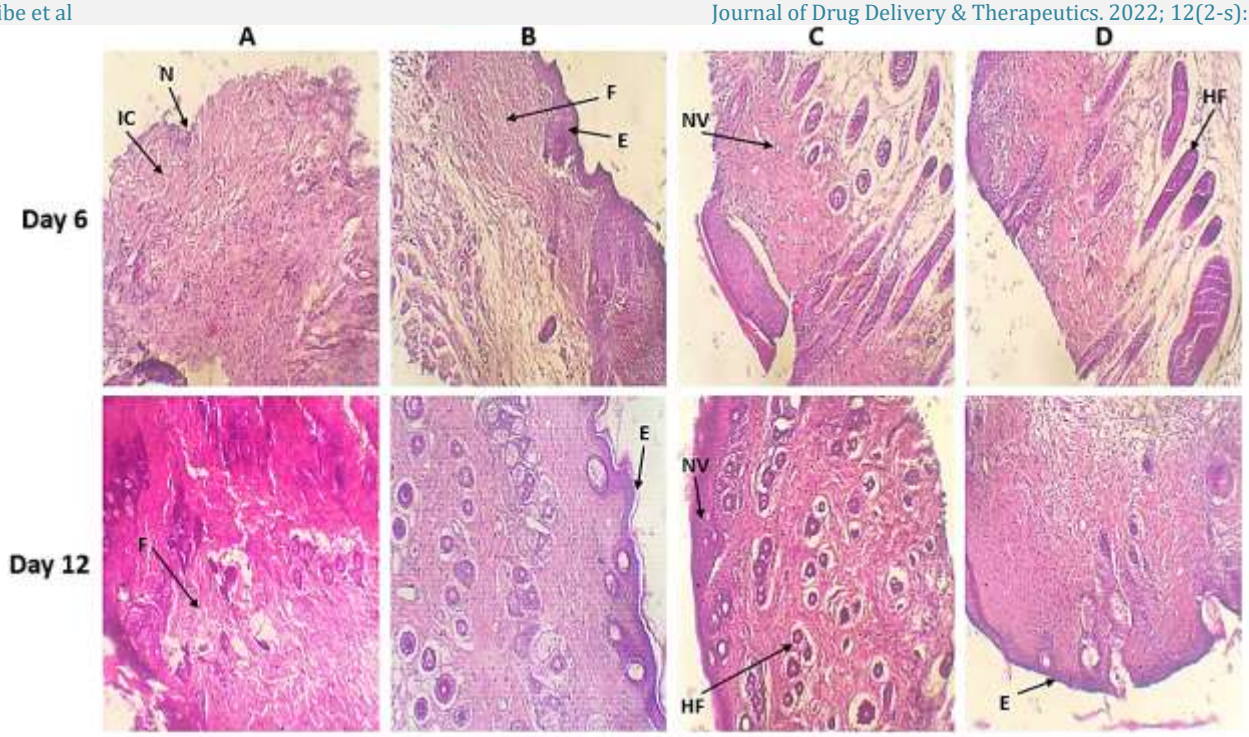

Figure 6: H&E-stained wound samples on days 6 and 12.

A= Gel control group, B= Gel + Leaves Extract 2.5 %, C= Gel + Leaves Extract 5 %, D= Brulex® (Zinc oxide 15% cream). N= Necrosis, IC = Inflammatory cells, HF = Hair follicles, F = Fibroblastic elements, NV = Neovessels, and E = Epithelialization. Magnification ×200.

Table 3: Summary of histological observations on day 6

	Components					
Treatments	**N**	**IC**	**HF**	**F**	**NV**	**E**
Gel control	+	++	-	-	-	-
Gel + LE 2.5 %	-	-	+	++	+	+
Gel + LE 5%	-	-	++	++	+	+
Brulex®	-	-	++	++	+	+

LE = Leaves Extract, N= Necrosis, IC = Inflammatory cells, HF = Hair follicles, F = Fibroblastic elements, NV = Neovessels, and E = Epithelialization. (-) = Absent, (+) = Minimal presence, (++) = Presence, (+++) = Marked presence.

Table 4: Summary of histological observations on day 12

	Components					
Treatments	**N**	**IC**	**HF**	**F**	**NV**	**E**
Gel control	-	-	+	++	++	++
Gel + LE 2.5 %	-	-	+++	+++	+++	+++
Gel + LE 5%	-	-	+++	+++	+++	+++
Brulex®	-	-	+++	+++	+++	+++

LE = Leaves Extract, N= Necrosis, IC = Inflammatory cells, HF = Hair follicles, F = Fibroblastic elements, NV = Neovessels, and E = Epithelialization. (-) = Absent, (+) = Minimal presence, (++) = Presence, (+++) = Marked presence.

DISCUSSION

The present investigation aimed to scientifically confirm the ethnomedicinal uses of *C. planchonii*. Its roots are the plant organ commonly used in pharmacopoeia to treat burn wounds. Differences in concentration of secondary metabolites from plant to plant species as well as in the different parts of a plant have been noted in various studies, leaves and roots being the preferential sites of accumulation of these compounds[20,21] However, in comparison with leaves, utilization of root parts highly affects the survival and ecological aspect of the plant so measures must be taken to protect these species. The leaves have then been included in later studies and have exhibited antibacterial properties similar to root extracts against bacteria often isolated from wounds[3]. The present data confirm that *C. planchonii* leaves share antioxidant and anti-inflammatory capacities that are closely similar to those of root extracts. No statistical

difference was found between animals treated with roots and leaf extracts of *C. planchonii* in models of acetic acid induced contortions, formalin induced edema and acetic acid induced vascular permeability. The antioxidant and anti-inflammatory capacities observed would be related to the metabolites (flavonoids, tannins, carbohydrates, sterols, triterpenes, and saponosides) found in the leaves and root hydroethanolic extracts of this plant and reported in our previous studies[3]. Polyphenolic compounds, in particular have well known antioxidant activities[22-25], antimicrobial activities[7,26], and anti-inflammatory properties[27-29].

This study, on the other hand, has also shown that leaf extract of *C. planchonii* can promote wound repair after skin burn injury in the rodent. Leaves extract 2.5 and 5 % mixed in Carbopol gel given topically have significantly accelerated the process of cicatrisation after 12 days when compared to a control group treated with the empty Carbopol gel. The utilization of *C. planchonii* leaves, which exhibited properties similar to roots, should then be promoted in order to protect this plant. A controlled agriculture operation of *C. planchonii* could also contribute to the economic development of the regions where it has been harvested.

CONCLUSION

The results revealed on one hand that both roots and leaf extracts tested share similar anti-inflammatory and anti-oxidant activities. On the other hand, we demonstrated that leaves extracts possess burn wound healing properties. These findings confirm the use of *C. planchonii* to manage burn wounds in traditional medicine in Togo. Our study, the first report on *C. planchonii* leaves burn wound healing activity, should be taken into account in the future political of long-lasting management of natural resources of Togo.

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Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this pape.

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