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EVALUATION OF ACUTE ORAL TOXICITY, ANTINOCEPTIVE AND WOUND-HEALING ACTIVITIES OF ETHANOLIC AND AQUEOUS ROOT EXTRACTS OF *COMBRETUM GLUTINOSUM* PERR. EX DC

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ABSTRACT: In Ivory Coast, the use of traditional medicinal plants is common because it's low cost and also the scarcity and expensive nature of hospitals for so-called modern drugs. In addition, different types of herbal and others are used to heal wounds. Among these medicinal plants, the root of *Combretum glutinosum* is strongly recommended by traditional activists even though their *in-vivo* wound healing activity is not reported. Phytochemical screening of *Combretum glutinosum* revealed the presence of sterols and polyterpenes, polyphenols, flavonoids, catechic tannins, gallic tannins, alkaloids, saponosides, anthraquinones terpenoids, and anthocyanins. Some researchers claim that these bioactive compounds obtained from the phytochemical analysis may be responsible for pharmaceutical activity. All plant extracts studied had LD_{50} values greater than 3000 mg/kg body weight and were therefore considered harmless. The study showed that the aqueous and ethanolic root extracts of *Combretum glutinosum* (AECG and EECG) have analgesic effects. Hence, they have the potential to offer safe pain-relieving compounds. The aqueous and ethanolic root extracts of *Combretum glutinosum*with Cocoa butter (AECG_25% and EECG_25%) have been shown to support traditional wound healing claims, as evidenced by an increase in the rate of wound contraction and tensile strength, thus translating to a decrease in wound healing.

INTRODUCTION: *Combretum glutinosum* Perr. Ex DC (Combretaceae family), is a small tree or bushy shrub, about 8 to 12 m high. The plant is present in Ivory Coast; it is called in Malinké "Naniaragbwé" and is used to treat common ailments including hepato-biliary ailments, urinary ailments, edema, arterial hypertension, cough, fever, malaria and spasms, diarrhea, dysentery, and constipation.

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The dried and crushed leaves are used in post-circumcision hemorrhages. The pounded roots are applied to the wounds. An infusion of the roots is used for washing wounds [1]. Wounds are major problems for poor populations who prefer treatment with medicinal plants. The majority of drugs currently available for the treatment of wounds are expensive; researchers need to intensify the botanical investigations in order to provide healing products that are affordable, effective, and safe [2].

Traditional African healers use medicinal plants such as *Combretum glutinosum* for its healing power. This study aims to characterize chemical groups, acute oral toxicity, analgesic effects and

wound healing activity in ethanolic and aqueous root extracts of *Combretum glutinosum*.

MATERIALS AND METHODS:

Plant Material: Dry roots of *Combretum glutinosum* were provided by a traditional therapist in July 2019 (Abidjan, Ivory Coast). It was identified and authenticated by the botanists of the laboratory. The roots were crushed, and a brown powder was obtained. The powder was stored in a jar.

Animals: The animals composed of albino mice and rats were supplied by the University animal store. They were fasted for 24 hours before the experiments and weighed periodically before and after each experiment.

Extraction of Plant: It is the technique of maceration employed to extract chemical elements present in the roots of *Combretum glutinosum.* Two solvents are used to carry out this kind of solid-liquid extraction, namely distilled water and ethanol [3].

Qualitative Phytochemical Screening: The qualitative phytochemical screening was performed on the two root extracts of *Combretum glutinosum* using the standard procedures described in **Table 1** to determine the phytochemicals [4]. AECG = Aqueous root extract of *Combretum glutinosum* and EECG = Ethanolic root extract of *Combretum glutinosum*.

TABLE 1: USUAL METHODS OF PHYTOCHEMICAL SCREENING

Secondary metabolite	Reagent of identification	Indicator (positive reaction)
Anthocyanin	H_2SO_4 and NH_4OH	Black color
Anthraquinones	NH_4OH	Yellow color
Saponins	Foam index	Persistent foam
Free quinones	NH_4OH	Red to purple color
Polyphenols	$FeCl_3$ (2%)	Dark blue or greenish color
Flavonoids	Hydrochloric alcohol, Magnesium shavings and Iso-amyl alcohol	Pink-orange or purplish color
Catechic tannins	Formalin and HCl	Gelatinous precipitate
Gallic tannins	Sodium acetate and $FeCl_3$	Blue-black color
Alkaloids	$HgCl_2$ and KI (Mayer)	Reddish-brown precipitate
	Picric acid (Hager) I_2 and KI (Wagner)	Creamy-white precipitate
Coumarins	KOH and HCl	Trouble or precipitate
Sterols and polyterpenes	Acetic anhydride acid and H_2SO_4	Color from purple to blue or green
Terpenoids	$CHCl_3$, H_2SO_4	Brown color
Mucilage	Absolute ethanol	Flocculent precipitate
Volatile oils	NaOH and HCl	Black color

Acute Oral Toxicity Study: The acute toxicity study was performed on aqueous and ethanolic root extracts of *Combretum glutinosum* (AECG and EECG) in accordance with OECD recommendations [5]. To begin with, a total of 25 mice (5 mice per batch) were randomly selected. The mice were divided into 5 groups of 5; GP 1: control (normal saline solution), GP 2: treated with 100 mg/kg bw, GP 3: treated with 250 mg/kg bw, GP 4: treated with 500 mg/kg bw, GP 5: treated with 3000 mg/kg bw. Careful observation was made to study changes in behavior and mortality for hours per time interval and then over a period of two weeks.

Antinociceptive Activity: The study of the analgesic effects of aqueous and ethanolic roots extracts of *Combretum glutinosum* were evaluated using the method of contortion induced by acetic acid on mice. A total of 50 mice (5 mice per batch) were randomly selected and marked for identification. The mice were divided into 10 groups of 5: GP 1: negative control (1.2 mL/100 g, distilled water), GP 2: positive control (150 mg/kg bw, Ibuprofen), GP 3: treated with 100 mg/kg bw of AEGC, GP 4: treated with 150 mg/kg bw of AEGC, GP 5: treated with 300 mg/kg bw of AEGC, GP 6: treated with 500 mg/kg bw of AEGC, GP 3 ': treated with 100 mg/kg bw of EEGC, GP 4': treated with 150 mg/kg bw of EEGC, GP 5 ': treated with 300 mg/kg bw of EEPO, GP 6': treated with 500 mg/kg bw of EECG. The mean number of writhes and the percentage

inhibition of writhes were calculated as an indicator of analgesic activity according to equation [6].

Percentage of writhing inhibition = (Wct-Wes) / Wct × 100

With Wct=the mean a number of writhes in the negative control and Wex = the mean number of writhes inthe experimental.

Wound-Healing Activity: The excision wound model and Incision wound model were used to assess the wound healing activity of aqueous and ethanolic roots extracts of *Combretum glutinosum* (AECG and EECG),

Excision Wound Model: A full-thickness circular excisional wound measuring approximately 500 mm^2 and 1.6 mm in depth was performed on the shaved dorsal thoracic region of the experimental rats while observing all laboratory safety guidelines. The rats were divided into 3 groups of 5: GP 1: placebo-control (Cocoa Butter), GP 2: treated with the ointment 25% of the aqueous root extracts of *Combretum glutinosum* (AECG_25%), GP 3: treated with the 25% ointment of the ethanolic root extract of *Combretum glutinosum* (EEGC_25%). The rate of wound closure was assessed by measuring the wound on days 0, 2, 4, 8, 12, 16, 18, and 20. The percentage of wound contraction at each time interval was calculated [7]:

Percentage of wound contraction = (Wound 0h - Wound th) / (wound 0h) × 100

With: wound 0h = wound area at 0 hour, wound th = wound area at particular time, t

Ointment's Formulation: One single ointment (cocoa butter) and two mixed ointments were prepared according to the formula described in **Table 2**. Cocoa butter, aqueous, and ethanolic root extract of *Combretum glutinosum*(AECG and EECG) and calcium benzoate (preservative = E213) were triturated in a mortar with a pestle to obtain a homogeneous paste. The AECG_25% and EEPO_25% ointments obtained were packaged in jars and stored at room temperature [8].

TABLE 2: COMPOSITION OF DIFFERENT OINTMENTS

Composition	Placebo Cocoa butter	Ointment AECG_25%	Ointment EECG_25%
AECG (g)	0	14	0
EECG (g)	0	0	14
Cocoa butter (g)	55	41	41
Calciumbenzoate (g)	1	1	1
Total (g)	56	56	56

Incision Wound Model: As with the previous model, a longitudinal paravertebral incision of 4 cm in length was made and sutured by 1 cm [9]. After 24 h of wound creation, the rats were divided into 3 groups of 6. GP 1: placebo-control (Cocoa butter + E 213), GP 2: treated with the 25% ointment of the aqueous root extract of *Combretum glutinosum* (AECG_25%), and GP 3: treated with the 25% ointment of the ethanolic root extract of *Combretum glutinosum* (EECG_25%). The sutures were removed on day 8 post-incision and the treatment was continued. Then, the tensile strength was measured on the 10th day and calculated using weight technique [10].

Percentage of tensile strength = (Tensile st exp-tensile st ct) / (Tensile st ct) × 100

With tensile st ct = the mean tensile strength of placebo control and tensile st exp = the mean the tensile strength of group treated.

Data Analysis: The experimental result was expressed as the standard error of the mean. The analysis of variance was used to compare the averages between more than two groups.

Values with $p < 0.05$ were considered statistically significant. Graphs were obtained using the Microsoft Excel 2013 spreadsheet. Statistical analyzes were performed in GraphPad Prism for Windows.

RESULTS:

Yield of Extracts: The percentage yield of ethanolic and aqueous root extracts of *Combretum glutinosum* is presented in **Table 3**.

TABLE 3: YIELD OF ETHANOLIC AND AQUEOUS ROOT EXTRACTS OF *COMBRETUM GLUTINOSUM*

Extract	Mass (g)	Yield (%)
EECG	4.45	8.90
EACG	5.25	10.50

Phytochemical's Analysis: Phytochemical screening of the ethanolic and aqueous root extracts of *Combretum glutinosum* (AEGC and EEGC) was done to qualitatively identify the presence or absence of secondary metabolites, and the results were presented in **Table 4**.

TABLE 4: RESULTS OF PHYTOCHEMICALS SCREENING

Secondary metabolite	AEGC	EEGC
Flavonoids	+	+
Gallic tannins	+	+
Free quinones	-	-
Saponins	+	+
Alkaloids	+	+
Coumarins	-	-
Anthraquinones	+	+
Terpenoids	+	+
Mucilages	-	-
Anthocyanins	+	+
Volatile oils	-	-
Catechic tannins	+	+
Cardiac glycosides	-	-
Sterols and polyterpenes	+	+
Polyphenols	+	+

+ = Positive means present, - = Negative means absent

Acute Oral Toxicity Study: The results of the oral acute toxicity study revealed that all tests of aqueous and ethanolic root extracts of *Combretum glutinosum* (AEPO and EEPO) were appeared safe to the dose of 3000 mg/kg as none of the mice was died and even did not show any.

Sign of toxicity during the observation period of 2 weeks. Therefore, LD_{50} of aqueous and ethanolic root extracts of *Combretum glutinosum*are greater than 3000 mg/kg.

Analgesic Study: The results of the analgesic effects of aqueous and ethanolic extracts are presented in **Table 5**. The aqueous and ethanolic root extracts of *Combretum glutinosum* showed significant analgesic activity. This activity reduced number of writhing induced by acetic acid **Fig. 1**.

TABLE 5: EFFECTS OF AEGC AND EEGC ON ACETIC ACID-INDUCED WRITHING

Groups	Writhing frequency	Inhibition of writhing (%)
GP 1: Negative control with 1.2 mL/100 g bw of Distilled water	95.71 ±1.65	0
GP 2: Positive control with 150 mg/kg bw of Ibuprofen,	10.91± 1.74	88.60
GP 3: Group treated with100 mg/kg bw of AEGC	38.12±1.35	60.17
GP 4: Group treated with150 mg/kg bw of AEGC	21.56±1.19	77.47
GP 5: Group treated with300 mg/kg bw of AEGC	08.39±1.56	91.23
GP 6: Group treated with 500 mg/kg bw of AEGC	05.58±1.49	94.17
GP 3': Group treated with100 mg/kg bw of EEGC	32.68±1.21	65.85
GP 4': Group treated with150 mg/kg bw of EEGC	17.69±1.42	81.52
GP 5': Group treated with300 mg/kg bw of EEGC	09.53±1.22	90.04
GP 6': Group treated with 500 mg/kg bw of EEGC	07.31±1.18	92.36

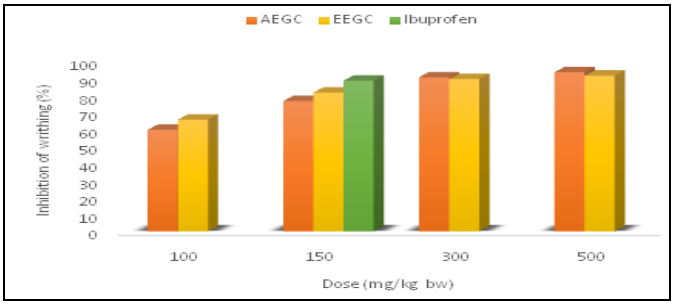

FIG. 1: COMPARISON BETWEEN THE EFFECTS OF AEGC, EEGC AND IBUPROFEN ON ACETIC ACID-INDUCED WRITHING

Wound-healing Activity:

Excision Wound Model: Based on the data in **Table 6**, AECG_25% and EECG_25% showed significant wound contraction compared to plain cocoa butter since the start of treatment.

The data in **Table 6** confirmed that a considerably shorter healing time was recorded by AECG_25% and EECG_25% compared to cocoa butter **Fig. 2**.

TABLE 6: WOUND-HEALING EFFECT OF COMBRETUM GLUTINOSUM IN EXCISION WOUND MODEL

Parameter Wound area (mm^2) and wound contraction (%)			
Post-wounding days	**Control**	**AECG_25%**	**EECG_25%**
Day 0	501.25 ± 1.28	502.30 ± 1.47	501.50 ± 1.42
Day 2	459.70 ± 1.34 (8.29%)	456.50 ± 1.21 (9.12%)	454.80 ± 1.38 (9.31%)
Day 4	414.80 ± 1.42 (17.25%)	389.90 ± 1.36 (22.38%)	382.50 ± 1.48 (23.73%)
Day 8	329.90 ± 1.41 (34.18%)	254.50 ± 1.47 (49.33%)	224.80 ± 1.54 (55.17%)
Day 12	209.50 ± 1.39 (58.20%)	104.80 ± 1.38 (79.13%)	96.76 ± 1.57 (80.70%)
Day 16	74.67 ± 1.43 (85.10%)	19.16 ± 1.23 (96.18%)	9.50 ± 1.29 (98.10%)
Day 18	19.35 ± 1.38 (96.14%)	3.57 ± 1.43 (99.29%)	00 ± 00 (100%)
Day 20	7.97 ± 1.24 (98.41%)	00 ± 00 (100%)	00 ± 00 (100%)
Period of epithelialization (day)	20.45 ± 1.50	18.35 ± 1.40	16.50 ± 1.50

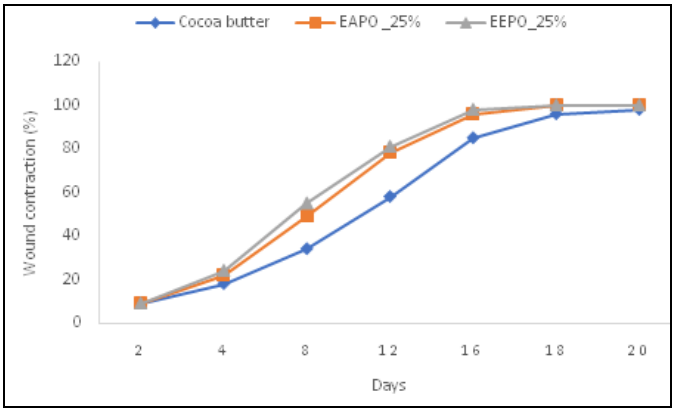

FIG. 2: WOUND AREA CONTRACTION (%) WITHCOCOA BUTTER, AECG_25%, EECG_25% IN EXCISION WOUND MODEL

Incision Wound Model: As shown in **Table 7**, AECG_25% and EECG_25% effectively increased the breaking strength of healing wound. Compared with Cocoa butter, AECG_25% and EECG_25% had a greater increasing effect on the tensile strength.

TABLE 7: WOUND-HEALING EFFECT OF COCOA BUTTER, AECG_25%, AND EECG_25% IN INCISION WOUND MODEL

	Breaking strength (g)	**Tensile strength (%)**
Cocoa butter	345.78±1.63	0
AECG_25%	538.14±1.58	55.63
EECG_25%	617.32±1.43	78.53

DISCUSSION: Phytochemical screening test of ethanolic and aqueous root extracts of *Combretum glutinosum* (EECG and AECG) revealed the presence of various secondary metabolites, including flavonoids, gallic tannins, saponins, alkaloids, anthraquinones, terpenoids, anthocyanins, catechic tannins, sterols, polyterpenes, and polyphenols. These biologically active compounds are responsible for antioxidant, anti-infective, antimicrobial, anti-inflammatory, antifungal, and anticancer activities [11, 12].

Flavonoids are sometimes used to try to promote the healing of leg ulcers. As for tannins, researchers claim that they encourage the wound healing process by promoting wound contraction [13, 14]. Based on the acute oral toxicity test results, the median lethal doses (LD_{50}) were greater than 3000 mg/kg. The ethanolic and aqueous root extracts of *Combretum glutinosum* (EECG and AECG) can be designated as safe [15].

During this method, acetic acid induces the release of mediators such as histamine, a biogenic amine acting as a chemical mediator of the inflammatory reaction. It is formed from the amino acid histidine. Histamine is released by the granules of basophilic granulocytes and by mast cells, for example, in the event of a cut in the skin or a microorganism. Histamine promotes vasodilation of blood vessels and their permeability [16]. Thus, in the event of a lesion, the coagulation proteins access the cut area more easily, which facilitates scarring and healing. At the cerebral level, the release of serotonin by acetic acid is involved in regulating many physiological functions: sleep, appetite, mood, anxiety, and pain in particular [17].

Bradykinin also plays an important role in pain; it is the most powerful allogenous substance released by the body's tissues during an injury: this pain-generating action appears even at low levels of concentration, which contributes to hyperalgesia. In this case, there are high levels of bradykinin in pain. Bradykinin works in synergy with other substances such as histamine and serotonin. It causes the release of other mediators and prostaglandins [6]. A wound can present different aspects, conditioning the healing. To manage a wound, two concepts are essential: its stage and its condition. There are four identified scarring stages: necrosis, fibrinous, budding, and epidermis [18]. It is

important to know that a wound evolves by following different states. It is, therefore, necessary to assess the state of the wound bed. There are also four well-identified conditions: dry, exuding, cavitary, and infected. The healing of a wound is an extremely complex phenomenon, specific to each organism. It involves the processes of repairing a localized lesion and regenerating tissue [19].

The physiological mechanisms of this process involve many cell types (fibroblasts and epithelial cells), successive cascades of intracellular messengers, and molecules involved in the general anabolism of organisms (GAG, fibronectin, collagen, *etc*.) [20]. These phenomena are regulated by growth factors and the interactions between the extracellular matrix and inflammatory cells. The healing of a wound turns out to be more or less long, depending on the patient. A duration which varies according to the nature of the wound (acute, chronic, superficial, deep), but also of the general state of health of the patient and even of his habits of life [21, 22].

CONCLUSION: Experiments have shown that the ethanolic and aqueous root extracts of *Combretum glutinosum* (EECG and AECG) have LD_{50} values greater than 3000 mg/kg and are non-toxic. Both AECG and EECG have been shown to be effective as analgesics or pain relievers. The present study indicated that cocoa butter had better wound healing activity with AECG_25% and EECG_25%.

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