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In vivo analgesic and healing activities of stem bark extracts of *Gardenia ternifolia* Schumach. & Thonn.

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ABSTRACT

In Ivory Coast, medicinal plants have always been used traditionally to promote wounds repairs. They have great potential for wound healing by promoting the speed of wound healing with less pain, discomfort and patient healing. The plant *Gardenia ternifolia* belongs to the family Rubiaceae. The macerated stem bark or the paste obtained is also used against bites snake, sexual impotence, hemorrhoids, healing wound, injury, and tooth decay. *Gardenia ternifolia* was extracted in aqueous and ethanol to evaluate acetic acid-induced writhing test to detect the peripheral analgesic activity of the extracts in mice. AEGT and EEGT showed reduced number of writhes which are significant compared to control (Acetaminophen). The results obtained support the use of *Gardenia ternifolia* in painful conditions acting peripherally. The healing activity of *Gardenia ternifolia* was also evaluated in the second part of the research. AEGT_50% and EEGT_50% ointments treated group showed a significant reduction in the wound breaking strength in incision type of wound model and significant increase in epithelization period and reduction in percentage of wound area in excision type of wound model as compared to control group treated with simple ointment.

Keywords: *Gardenia ternifolia*, Analgesic, Wound healing, AEGT, EEGT.

INTRODUCTION

Gardenia ternifolia Schumach. & Thonn. is an evergreen savanna shrub or small tree up to 6 m tall. The stem bark is greyish white and smooth. It is thick, brittle, hairless but covered on the outside with a dusty greyish coating under which the green color of the bark appears. Wood is very difficult to cut [1, 2]. Native to the tropics to subtropics of South Asia, Australia and Oceania, *Gardenia ternifolia* is a species that has also been found in several African countries. It is present in Côte d'Ivoire, Senegal, Sudan, Mali, Guinea, Liberia, Niger, Nigeria, Sierra Leone, Ghana, Togo, Benin, and Cameroon. The stem bark is used for the treatment of asthma, infectious pathologies including those sexually transmitted (syphilis), malaria, laxative, skin diseases, hypertension, diabetes, cough, rheumatism, diarrhea, tooth decay, leprosy, hernia, hemorrhoids, healing wound, injury and cancer [3, 4, 5]. *Gardenia ternifolia* is a plant common to several African pharmacopoeias however there are no work has been published on the analgesic effect and the wound healing activity of stem bark of *Gardenia ternifolia* so it becomes imperious to make this study.

MATERIALS ET METHODS

Plant material and extraction

The stem bark of *Gardenia ternifolia* Schumach. & Thonn. was collected in a forest in the village of Abatta (Abidjan, Côte d'Ivoire) in July 2020. It was identified and authenticated in the National Floristic Center of the University of Félix Houphouët Boigny, Cocody -Abidjan, Department of Botany, Ivory Coast where voucher specimens were deposited (Herbarium Voucher Number: CNF-14149). First, the fresh stem bark of the plant was cut and broken into small pieces and oven dried. The preparation of the extracts was done by the standard cold maceration extraction method because the heat destroys the active constituents of the medicinal plant, cold maceration is more suitable than a decoction. Two solvents of different polarity are used, namely distilled water and ethanol. The maceration was then filtered, and the filtrate was dried in a hot air oven set at 80 °C for 24 h and weighed again [6].

AEGT = Aqueous stem bark Extract of *Gardenia ternifolia*
EEGT = Ethanolic stem bark Extract of *Gardenia ternifolia.*

Animal material

Adult albino mice of both sexes were obtained from the University pet store. the mice were acclimatized

to the environment for a week before the launch of the experiment. All procedures were performed according to standard guidelines for care and the use of laboratory animals. The experimental protocol has been approved by the laboratory.

Phytochemical screening

The aqueous and ethanolic extracts of the stem bark of *Gardenia ternifolia* were subjected to a qualitative phytochemical study to detect the different chemical families, Table 1.

AEGT and EEGT were subject to the identification by precipitation reaction and staining according to the methodology of the phytochemical screening [7].

Table 1: Phytochemical study

Phytocompounds	Reagent of identification	Indicator (positive reaction)
Saponosides	Foam index	Persistent foam
Flavonoids	Hydrochloric alcohol, Magnesium shavings and Iso-amyl alcohol	Pink-orange or purplish color
Anthocyanin	H_2SO_4 and NH_4OH	Black color
Terpenoids	$CHCl_3$, H_2SO_4	Brown color
Polyphenols	$FeCl_3$ (2%)	Dark blue or greenish color
Anthraquinones	NH_4OH	Yellow color
Catechic tannins	Formalin and HCl	Gelatinous precipitate
Gallic tannins	Sodium acetate and $FeCl_3$	Blue-black color
Free quinones	NH_4OH	Red to purple 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
Mucilage	Absolute ethanol	Flocculent precipitate
Volatile oils	NaOH and HCl	Black color
Cardiac glycosides	$CHCl_3$, H_2SO_4	Brown color

***In vivo* Analgesic Activity**

The study of the analgesic effects of aqueous and ethanolic stem bark extracts of *Gardenia ternifolia* were evaluated using the method of writhing induced by acetic acid on mice. First, a total of 60 mice (6 mice per batch) were randomly selected and marked for identification. The mice were divided into 10 groups of 6: Group 1: negative control (10 mL/kg, distilled water), Group 2: positive control (85 mg/kg bw, Acetaminophen), Group 3: treated with 21.25 mg/kg bw of AEGT, Group 4: treated with 42.5 mg/kg bw of AEGT, Group 5: treated with 85 mg/kg bw of AEGT, Group 6: treated with 170 mg/kg bw of AEGT, Group 7: treated with 21.5 mg/kg bw of EEGT, Group 8: treated with 42.5 mg/kg bw of EEGT, Group 9: treated with 85 mg/kg bw of EEGT, Group 10: treated with 170 mg/kg bw of EEGT. The mean number of writhes and the percentage inhibition of writhes were calculated as an indicator of analgesic activity according to equation [8].

$$\text{Percentage inhibition of writhing} = \frac{\text{writhes ctrl} - \text{writhes expt}}{\text{writhes ctrl}} \times 100$$

With writhes ctrl = the mean number of writhes in the control and writhes expt = the mean number of writhes in the experimental

***In vivo* Healing activity**

To assess healing activity of aqueous and ethanolic stem bark extracts of *Gardenia ternifolia* (AEGT and EEGT), standard models of excisional and incisional wounds were used.

Excision wound model

A full-thickness circular excisional wound measuring approximately 250 mm^2 and 1.5 mm in depth was performed on shaved dorsal thoracic region of experimental rats while respecting all laboratory recommendations. The mice were divided into 3 groups of 6: Group 1: placebo control (Shea butter), Group 2: treated with 50% ointment of the aqueous stem bark extract of *Gardenia ternifolia* (AEGT_50%), Group 3: treated with 50% ointment of the ethanolic stem bark extract of *Gardenia ternifolia* (EEGT_50%). The wound closure rate was assessed by measuring wound on days 0, 2, 4, 8, 12, 16, 18, and 20. The percentage of wound contraction at each time interval was calculated [9]:

$$\text{Percentage of wound contraction} = \frac{\text{wound 0} - \text{wound t}}{\text{wound 0}} \times 100$$

With: wound 0 = wound area at 0 hour,

Wound t = wound area at particular time (t)

Ointment's formulation

A single ointment (shea butter) and two mixed ointments were prepared according to formula described in Ivorian Pharmacopoeia (Table 2) and (Figure 1). Shea butter, stem bark extract aqueous and ethanolic of *Gardenia ternifolia* (AEGT and EEGT), and Calcium benzoate (preservative = E 213) were triturated in a mortar with a pestle to obtain a homogeneous paste. Two ointments, AEGT_50%

and EEGT_50% were packaged in jars and stored at room temperature [10].

Table 2: Formula used for different ointments

Composition	Placebo Shea butter	Ointment AEGT_50%	Ointment EEGT_50%
AEGT (g)	0	22.875	0
EEGT (g)	0	0	22.875
Shea butter (g)	45.75	22.875	22.875
Calcium benzoate (g) (E 213)	0.25	0.25	0.25
Total (g)	46	40	40

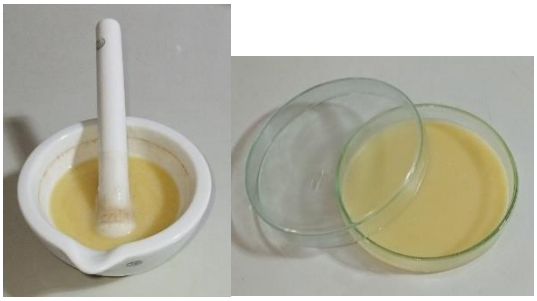

Figure 1: Ointment AEGT_50%

Incision wound model

Under the same conditions as for the previous model, a longitudinal paravertebral incision of 5 cm in length was made and sutured by 1 cm this time. After 24 h of wound creation, on the first day, the mice were divided into 3 groups of 6. Group 1: placebo control (Shea butter + E 213), Group 2: treated with the 50% ointment of the aqueous stem bark extract of *Gardenia ternifolia* (AEGT_50%), and Group 3: treated with the 50% ointment of the ethanolic stem bark extract of *Gardenia ternifolia* (EEGT_50%). 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 [11].

$$\text{Percentage of tensile strength (PTS)} = \frac{\text{tensile strength expt} - \text{tensile strength ctrl}}{\text{tensile strength ctrl}} \times 100$$

with tensile strength ctrl = the mean tensile strength of placebo control and tensile strength expt = the mean the tensile strength of group treated

Data analysis

The experimental result was expressed as 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 2016 spreadsheet. Statistical analyzes were performed in GraphPad Prism for Windows.

RESULTS

Yield of extracts

The percentage yield of ethanolic and aqueous stem bark extracts of *Gardenia ternifolia* (AEGT and EEGT) was presented in Table 3.

Table 3: Yield (%) of ethanolic and aqueous stem bark extracts of *Gardenia ternifolia*

Extract	Mass (g)	Yield (%)
EEGT	5.7	11.40
EAGT	6.9	13.80

Phytochemical screening

Phytochemical screening of the ethanolic and aqueous stem bark extracts of *Gardenia ternifolia* (AEGT and EEGT) was done to qualitatively identify presence or absence of secondary metabolites and results were presented in Table 4.

Table 4: Results of phytochemicals analysis

Secondary metabolites	EEGT	EAGT
Alkaloids	Presence	Presence
Anthraquinones	Absence	Absence
Anthocyanins	Presence	Presence
Catechic tannins	Presence	Presence
Gallic tannins	Presence	Presence
Free quinones	Absence	Absence
Saponins	Presence	Presence
Sterols and polyterpenes	Presence	Presence
Coumarins	Absence	Absence
Polyphenols	Presence	Presence
Terpenoids	Presence	Presence
Mucilages	Absence	Absence
Flavonoids	Presence	Presence
Volatile oils	Absence	Absence
Cardiac glycosides	Absence	Absence

***In vivo* analgesic effects**

The result of the analgesic effects AEGT and EEGT is presented in Table 5. AEGT and EEGT showed significant analgesic activity in reducing number writhing induced by acetic acid (Figure 2).

Table 5: Effects of AEGT and EEGT on acetic acid-induced writhing in mice

Groups	Treatment	Dose	Writhing frequency	Percent inhibition (%)
Group 1	Distilled water	10 mL/kg	75.65±1.37	0
Group 2	Acetaminophen	85 mg/kg	13.78±1.21	81.78
Group 3	AEGT	21.5 mg/kg	47.17±1.18	37.65
Group 4	AEGT	42.5 mg/kg	27.75±1.44	63.32
Group 5	AEGT	85 mg/kg	12.79±1.83	83.09
Group 6	AEGT	170 mg/kg	09.15±1.46	87.90
Group 7	EEGT	21.5 mg/kg	48.16±1.27	36.34
Group 8	EEGT	42.5 mg/kg	29.71±1.45	60.73
Group 9	EEGT	85 mg/kg	13.22±1.63	82.52
Group 10	EEGT	170 mg/kg	10.81±1.33	85.71

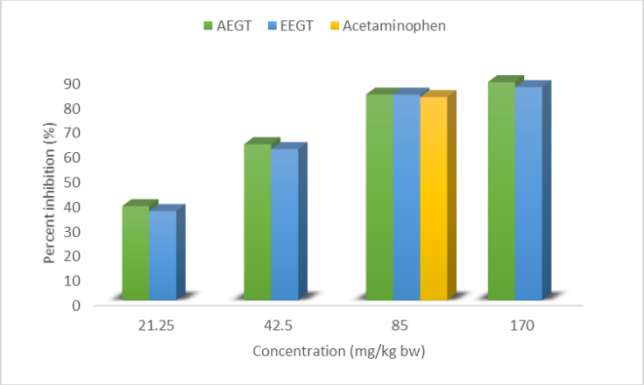

Figure 2: Comparison between the effects of AEGT, EEGT and Acetaminophen on acetic acid-induced writhing in mice

***In vivo* Healing activity**

Excision wound

AEGT_50% and EEGT_50% showed significant wound contraction against control placebo on day 2 to day 20. The data from (Table 6) confirmed that considerably shorter healing time was recorded by EEGT_50% and AEGT_50% ointments against control placebo (simple ointment) (Figure 4).

Table 6: Wound-healing effect of Simple ointment (Control placebo), AEGT_50% and EEGT_50% ointments in excision wound model

Wound area (mm^2) and Wound contraction (%)			
Post-wounding days	**Group 1: Control placebo**	**Group 2: AEGT_50%**	**Group 3: EEGT_50%**
0	250.00 ± 1.21	250.00 ± 1.34	250.00 ± 1.15
2	235.75 ± 1.42 (05.70%)	218.57 ± 1.13 (12.57%)	203.80 ± 1.24 (18.48%)
4	205.69 ± 1.10 (17.72%)	157.90 ± 1.51 (36.84%)	101.55 ± 1.10 (59.38%)
8	190.89 ± 1.50 (23.64%)	88.59 ± 1.43 (64.56%)	71.95 ± 1.70 (71.22%)
12	123.50 ± 1.34 (50.60%)	48.76 ± 1.20 (80.49%)	11.56 ± 1.17 (95.37%)
16	107.15 ± 1.24 (57.14%)	09.16 ± 1.33 (96.33%)	00 ± 00 (100%)
18	81.59 ± 1.20 (67.36%)	00± 00 (100%)	00 ± 00 (100%)
20	23.97 ± 1.27 (90.41%)	00 ± 00 (100%)	00 ± 00 (100%)
Epithelialization (day)	21 ± 1.82	17 ± 1.29	13 ± 1.64

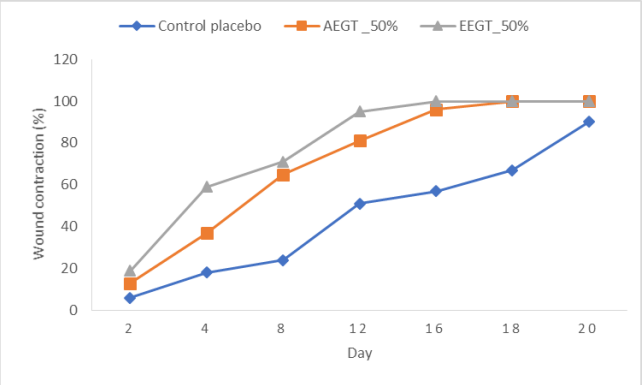

Figure 3: Wound-healing effect of AEGT_50%, EEGT_50% and Control placebo in excision wound model

Incision wound

As shown in Table 7, AEGT_50% and EEGT_50% were effective in increasing breaking strength of healing wound. Comparing with Control placebo (simple ointment), AEGT_50% and EEGT_50% had a greater increasing effect on the tensile strength.

Table 7: Wound-healing effect of Control placebo (simple ointment), AEGT_50% and EEGT_50% in incision wound model (Tensile Strength Model).

Groups	Wound breaking strength (g)	Tensile strength (%)
Group 1: Control placebo	225.15±1.25	0
Group 2: AEGT_50%	374.54±1.18	66.35
Group 3: EEGT_50%	418.35±1.63	85.80

DISCUSSION

Phytochemical screening test of AEGT and EEGT revealed the presence of various secondary metabolites including anthocyanins, catechics tannins. polyterpenes, sterols, triterpenoids, alkaloids, flavonoids, saponins, gallic tannins, and polyphenols. These biologically active compounds are directly accountable for antioxidant, detoxification, antiplasmodial, antimicrobial, anti-inflammatory, cytotoxic, antifungal, hypotensive, and anticancer activities [12]. Tannins and alkaloids are well known for their ability to inhibit pain perception and may be responsible for the studied analgesic activity [13]. Flavonoids were reported to have a role in analgesic activity primarily by targeting prostaglandins (PGs) [14].

Acetic acid induced writhing in mice attributed pain finds much attention of screening analgesic drugs. AEGT and EEGT showed significant analgesic action compared to the reference drug Acetaminophen but AEGT was found to exhibit higher analgesic activity than EEGT against acetic acid induced pain in mice. Pain sensation in acetic acid induced writhing method is elicited by triggering localized inflammatory response resulting release of free arachidonic acid from tissue phospholipid via cyclooxygenase (COX), and prostaglandin H_2 (PGH_2) [15]. AEGT and EEGT inhibits the enzyme prostaglandin synthetase in the peripheral nervous system, thus reducing the amount of prostaglandins formed by reducing the sensation of pain. From our results, AEGT and EEGT are the agents reducing the number of writhing by inhibition of prostaglandin synthesis, a peripheral mechanism of pain inhibition acting in the same way as acetaminophen [16]. Intraperitoneal injection of acetic acid causes irritation and stimulation of the peritoneal cavity that triggers the synthesis and release of various endogenous inflammatory mediators such as histamine (vasodilator), serotonin (neuromodulator), bradykinin (vasodilator) substance P (neuromodulator and neurotransmitter), and prostaglandins (hormone) [17].

During healing, contraction plays a crucial role as it decreases the dimension of the wound and hence shortens the healing time. Increased rate of wound contraction and decrease in epithelialization period in mice treated with AEGT_50% and EEGT_50% ointments may be attributed to the presence of phytoconstituents such as anthocyanins, catechics tannins. polyterpenes, sterols, triterpenoids, alkaloids, flavonoids, saponins, gallic tannins, and polyphenols compounds which are known to promote the wound healing process [18].

Acute wounds and chronic wounds have different healing times. Acute wounds (burns, cuts, abrasions, etc.) thus heal faster (between 2 and 4 weeks) than chronic wounds. However, the chronic wound is often linked to an underlying disease such as diabetes, venous or arterial insufficiency. Its healing requires 210 days, or nearly 7 months [19].

The healing process is broken down into 3 stages where each one plays an essential role on the road to recovery.

The debridement phase: immediately after the injury, an impressive cellular mechanism is set in motion. Then begins a cleaning process. The wound gets rid of devitalized or damaged tissue, which is now useless in its role, that of protecting the body. This inflammatory phase is exacerbated in chronic wounds. The wound can sometimes become covered with a yellowish layer which requires a suitable local treatment to get rid of the dead tissue.

The budding phase: then the repair process follows its course with this new stage. The wound takes on a less smooth, grainy appearance. Indeed, a multitude of small formations gradually fill the wound. Its red and shiny coloring is explained by the intensive production of collagen and the manufacture, by the body, of new blood vessels. these will replace those that have been destroyed.

The epidermis phase: little by little, the wound subjected to contractions finally closes. Its appearance is drier. Finally, a new skin, initially pinkish and fragile, gradually forms, until it covers the entire wound that has become a scar [20]. The latter will remain clearer than the surrounding skin, until the melanin-laden cells responsible for the color appear, sometimes for months or even never [21].

CONCLUSION

In conclusion, AEGT and EEGT were found to have significant analgesic activity in acetic acid induced writhing test. The different phases of wound repair; wound contraction, epithelization, and tensile strength were improved by AEGT_50% and EEGT_50% ointments as compared to the simple ointment (Shea butter + E 213) treated group. The findings of this study therefore support the traditional claims of *Gardenia ternifolia* Schumach. & Thonn. for wound treatment and pain.

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Conflict of Interest

None declared.

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None declared.

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