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Original Research Article

Antibacterial Activity of *Lantana camara montevidensis* Leaf Extract on Wound Isolates Using Animal Models

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ABSTRACT

Many communities in Nigeria and other African countries use plants to treat various infections, including wounds. This study was aimed to determine the antibacterial activity of *Lantana camara* montevidensis leaf extract on wound isolates using animal models. *Lantana camara* leaves were shade-dried, pulverized and extracted by Soxhlet method in methanol and water before standardization for use. Extract concentrations of 100 µg/mL, 50 µg/mL, 25 µg/mL and 12.5 µg/mL were prepared for topical treatment of the Wistar rats' incision wounds. Thirty healthy mature male Wistar rats weighing 120-170 g were used for this study. All the animals were wounded by making incisions on the neck region close to the scapula with initial wound area of 20.0 mm^2. *Pseudomonas aeruginosa* and *Staphylococcus aureus* were introduced into each wound incision. Results revealed that the susceptibility rate to antibiotics ranged from 10.0% – 70.0%. The susceptibility rate of the bacterial isolates to different concentrations of the extract (100, 50, 25 and 12.5 µg/mL) ranged from 0.0 – 60.0%. The isolates were most susceptible to 100 µg/mL methanol extract but were all resistant to the aqueous extract. Methanol extract had broad spectrum antimicrobial activity on wound isolates. Histologically, there was damaged tissue repair indicated by the presence of fibrocollagen formation with mild inflammatory cells. Therefore, *Lantana camara montevidensis* crude extract may be used for bacterial wound infection management.

***Keywords*:** Bacteria, Extract, Infection, *Lantana camara* montevidensis, Wound.

Introduction

Lantana camara (*verbenaceae*) is an ever-green perennial plant with some characteristic odour.[1] Its height is about 3m; it also grows up with or without minute prickles on the branches. Pandithurai*et al.*[2] reported that *L. camara* is an important source of different classes of phytochemicals such as steroids, flavonoids, oligosaccharides, triterpenoids, glycosides and naphthoquinones. Various important phyto-molecules such as oleanolic acid, lantanoside, linaroside, verbanoside, usolic acid, camaranic acid, umuhengerin and phyol have been isolated from *L. camara* and their biological actions such as anticancer, antioxidant, hepatoprotective, leishmanicidal, antibacterial, nematicidal and antiulcer have been reported. *Lantana camara* leaves are easily accessible at low or no cost in resource poor communities where species are found.[3-5]
Wounds are the third most frequent nosocomial infections.[6] They can increase the time for healing process leading to prolong hospital stay.[7-8] In developing and resource-poor countries, traumatic and surgical site infections are reasons for high morbidity and mortality rates.[9-11]
Regional and local variations occur among causative micro-organisms.[12-13] *Staphylococcus aureus* and *Pseudomonas aeruginosa* have been reported in several studies as common wound pathogens.[7]With the surge of multi-resistant bacteria, health care providers have become increasingly challenged in effective wound management.[12-13]

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There is an upward increase in antimicrobial resistance among microorganisms, due to indiscriminate use of antibiotics especially in the developing world.[11] This study on the natural product, *Lantana camara* leaf extract on incision wounds on albino Wistar rats could serve as an alternative source or new agent with pharmacological potential that could be more efficient against wound pathogens and less toxic to the human body. This study aimed to determine the antimicrobial activity of *Lantana camara* leaf extract against selected clinical bacterialisolates from infected wounds in vivo using animal models.

Plate1: *Lantana camara* montevidensis plant

Materials and Methods

The study was a prospective experimental study which ran for 18 months from October 2017 to March, 2019. *Lantana camara* leaves (Plate 1), were plucked from hedges in June, 2018 and identified by a botanist in the Department of Biology, Cross River University of Technology (CRUTECH), with Voucher number: Bot/Herb/Ucc/062.

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Lantana camara leaf extraction

The shade-dried leaves was pulverized and extracted by Soxhlet method in alcohol and water before standardization. Extraction by Soxhlet method was done in the Department of Pharmacology, University of Calabar, and standardized accordingly. The leaves (500 g) were shade-dried, pulverized and packed. The dried powdered leaves (25g) were filled in the thimble and extracted successively with absolute methanol (250mL) for 24 hours. Finally, the flask containing a deposit and a little of the methanol was evaporated and 10g of extract was collected. The same procedure was repeated using water as the solvent.

Animals for the *in vivo* studies were raised after obtaining approval from the Faculty Animal Research Ethics Committee, Faculty of Basic Medical Sciences (FAREC-FBMS) With No: 003MLS20418, University of Calabar, Nigeria.

Known clinical isolates from wound infections were obtained from the Microbiology/Parasitology Laboratory, University of Calabar Teaching Hospital for *in vitro* and *in vivo* analysis. The isolates include: *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The isolates were maintained as stock in Nutrient agar slants. Each isolate was sub cultured on the appropriate culture media at 37^0C for 24 hours before use. The Kirby-Bauer (disc diffusion) method was used to determine the antibiotic susceptibility of isolates.[14]Different concentrations of the plant extract were incorporated onto 6 mm in diameter disc. The discs were dried at 37°C and controlled before use. The different disc concentrations were 100, 50, 25 and 12.5 µg. The various concentrations of the leaf extract on the discs was used to determine the susceptibility of isolates by Kirby-Bauer method. The minimum inhibition concentration (MIC) and Minimum bactericidal concentration (MBC) was determined.[15-16]

Extract preparation for wounds

The following concentrations were prepared for topical treatment of the incision wounds on the Wistar rats. The methanol leaf extract (1 g) was dissolved in 10 mL of distilled water. This is equivalent to 100 mg/mL of the extract. The target concentrations of the extract for the topical applications were 100 mg/mL (high dose), 50 mg/mL (medium dose) and 25 mg/mL (low dose). One in 2 dilution of this stock in distilled water contained 50 mg/mL of the extract. The desired concentration for each group was applied as 0.1 mL topically. The wound were monitored for 21 days before the animals were sacrificed and skin sections obtained for histopathology testing.[17]

The antibiotics used as controls; Ofloxacin, Ciprofloxacin, Ceftriaxone, Doxycycline and Erythromycin were also diluted to the corresponding concentrations 100 (high dose), 50 (medium dose) and 25µg/mL (low dose), before application.[17]

Preparation of bacterial inoculum

Brain Heart Infusion Broth (BHIB) was used for bacterial growth. The inoculum was incubated for 24 hours at 37ºC. The overnight broth culture of each clinical isolate was diluted in the same media to a final concentration of approximately 1 x 10^8 Cfu/mL which is equivalent to 0.5 McFarland standard.[15]

Experimental animals

Thirty healthy mature male albino Wistar rats weighing 120-170g were used for this study. The animals were allowed to access food and water throughout the period. The experiment was designed to assess the physical and histological effect of wound healing using methanol extract of *L. camara* leaf for 21 days. The animals were divided into two groups of fifteen rats each. Three of the rats in each group were treated with different concentrations of the extract, antibiotics (positive control) and the last three were left untreated (negative control).

Group A: The animals were given wound incisions and inoculated with *Pseudomonas aeruginosa* isolate. Three rats each were treated with different concentrations (100µg/mL, 50µg/mL and 25µg/mL) of the *L. camara* montevidensis extract topically. Three rats were treated with 100µg/mL of ofloxacin (control) while the fifth group of three rats was left untreated (negative control).

Group B: The animals were given wound incisions and inoculated with *Staphylococcus aureus* isolate. Three rats were treated with different concentrations (100µg/mL, 50µg/mL and 25µg/mL) of the *L. camara montevidensis* extract topically as described above. The control group was treated with 100µg/mL of ofloxacin while the fifth group was left untreated.[10]

Creation of infected wound models and topical application of extract and antibiotics

Day 1

The animals were shaved using sterile razor blade. After removal of hair, skin swab culture was done on all the rats to confirm the absence or presence of the isolates under study. All the animals were wounded by making incisions of about 2.0cm long and 1.0cm wide at the neck region close to the scapula giving an initial wound area of 20.0mm^2. After 40 min, 0.5 mL of the inoculum of the clinical isolates; *Pseudomonas aeruginosa* and *Staphylococcus aureus* were introduced into each wound incision.[17]

Day 2

Before treatment with the different concentration of the extract, wound swabs were obtained for culture to confirm presence or absence of the isolate introduced. The wounds were cleaned with swabs soaked in distilled water before applying 0.1 mL of the different concentration of extracts and antibiotics topically.

Day 3 – Day 21

The same process for day 2 was carried out. The wounds were physically observed for healing. The wound size was measured on day 7, 14 and 21. The Wistar rats were sacrificed on day 21. Tissue sections of the lesions were obtained for histological examination. The wound areas were cut and preserved in alcohol before histological examination was carried out.[18]

Measuring of wound healing process

The wound area was traced on a transparent film on day 7, 14 and 21 respectively. The tracing was evaluated for surface area in mm^2. The percentage of wound contractions was calculated as follows:

$$\% \text{ of wound contraction} = \frac{\text{Initial wound size} - \text{Specific day wound size}}{\text{Initial wound size}} \times 100.$$ [19]

Statistical analysis

Data obtained from the study was analyzed using Epi Info 2010 (CDC, Alanta, Georgia, USA) Statistical Software. Descriptive statistics was carried out. Frequency was calculated for categorical variables. Interaction between specific categorical variables was tested for significance using Chi square test. Analysis of variance was performed to test whether group variance was significant or not. A p value of $\leq$ 0.05 was considered statistically significant.

Results and Discussion

Susceptibility pattern of bacterial isolates to selected antibiotics

Table 1 shows the susceptibility rates of the clinical isolates from wounds against selected commonly used antibiotics. The susceptibility rate for the bacterial isolates ranged from 10.0% – 70.0%. *Pseudomonas aeruginosa* and *Staphylococcus aureus* were most susceptible to ofloxacin with 50.0 and 70.0% susceptibility rates followed with Ceftriaxone with 40.0 and 30.0% susceptibility respectively. Erythromycin was not tested on *P. aeruginosa* because it is not indicated for the organism.

Figure 1 shows the susceptibility rates of *Staphylococcus aureus* to methanol and aqueous extract of *Lantana camara* leaf at different concentrations; 100, 50, 25 and 12.5µg/mL. The susceptibility rates ranged from 0.0 – 60.0%. Figure 2 shows the susceptibility rates of *Pseudomonas aeruginosa* to methanol and aqueous extract of *Lantana camara*leaf at different concentrations; 100, 50, 25 and 12.5µg/mL. The susceptibility rates ranged from 0.0 – 40.0%. *Pseudomonas aeruginosa* and *Staphylococcus aureus* were most susceptible to the

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100 µg extract with 40.0 and 60.0% susceptibility rate respectively. The bacterial isolates were not susceptible to 25 and 12.5 µg extract.

Table 2 shows the mean wounds contractions on Wistar rats inoculated with *Pseudomonas aeruginosa.*

There was significant difference in the mean wound contraction with 100 mg/mL of extract treatment.Table 3 shows mean wound contractions on Wistar rats inoculated with *Staphylococcus aureus*. There was significant difference in the mean wound contraction with 100 mg/mL of extract treatment.The antimicrobial activity of *Lantana camaramontevidensis* leaf extract on selected clinical bacterial isolates associated with wound infections was tested invitro and in vivo. The activity of *Lantana camara* leaf extracts varies with the solvent of extraction. The activity of alcohol extracts over water extracts have been reported in several studies.[20-21] In this study, *Lantana camara monte videnses* methanol leaf extract was tested invitro on wound isolates and in vivo on induced wounds on albino Wistar rats.The methanol leaf extract exhibited antibacterial activity against the gram positive bacteria, *Staphylococcus aureus* and gram negative bacteria, *Pseudomonas aeruginosa* at concentrations of 100 µg and 50 µg. The 25µg and 12.5µg concentrations of the extract had no effect on the bacterial isolates. The MIC of the leaf extract to *Staphylococcus aureus* and *Pseudomonas aeruginosa* was 0.312 and 0.0390 µg/mL respectively. Barreto *et al*[15] in Cariri-Ceara, Brazil reported that *L. camara* leaf extract was effective against *Staphylococcus aureus* at MIC 128 µg/mL and *Pseudomonas aeruginosa* at MIC 8 µg/mL. This difference in the strength could be due to the fact that their isolates were American Type Culture Collection isolates while the isolates in this study were known isolates obtained from wounds.The methanol leaf extract showed a range of inhibition on the bacterial isolates tested. The susceptibility rates ranged between (0.0% – 60.0%) with the 100µg concentration being the most effective. The isolates were all resistant to the different concentration of aqueous extract. This finding is in agreement with the work of Ashish*et al*[22] and Jabbar*et al*[20] who reported that *P. aeruginosa* and *S. aureus* were susceptible to *Lantana camara* leaf extract at various concentrations. Nayak*et al.*[17] in Trinidad also reported that *L. camara*crude extract had antimicrobial activity against *Staphylococcus aureus.*Antibiotic susceptibility of isolates to commonly used antibiotics was low. The low susceptibility of isolates observed in this study, agrees with the reports of Ogba *et al.*[7] in Nigeria and Anguzu and Olila[9] in Uganda. The multiple antibiotic resistance of isolates, especially *S. aureus* and *P. aeruginosa* to quinolones and Cephalosporins which are commonly used in our locality calls for an immediate action on the controlled use of antimicrobials in the hospitals and the need to monitor resistance.

Table 1: Susceptibility pattern of bacterial isolates to antibiotics

Clinical isolates	No. tested	Antibiotics tested				
		No. (%) of isolates susceptible				
		OFX	CIP	CFTR	DOX	ERY
Pseudomonas aeruginosa	10	5(50.0)	3(30.0)	4(40.0)	1(10.0)	NT
Staphylococcus aureus	10	7(70.0)	2(20.0	3(30.0)	0(0.0)	2(20.0)

OFX – Ofloxacin, CIP – Ciprofloxacin, CFTR – Ceftriaxone, DOX – Doxycycline
ERY - Erythromycin

Table 2: Mean wounds contractions on Wistar rats inoculated with *Pseudomonas aeruginosa*

Days	100 µg/mL (n=3)	50 µg/mL (n=3)	25 µg/mL (n=3)	Ofloxacin (100µg/mL) (n=3)	No treatment. (n=3)	P-Value
Day 7	35.00 ± 0.00^{a}	24.67 ± 0.58^{b}	11.00 ± 1.00^{c}	50.33 ± 0.53^{d}	4.33 ± 0.57^{e}	0.000
Day 14	63.67 ± 1.53^{a}	41.33 ± 1.53^{b}	24.67 ± 0.58^{c}	64.00 ± 1.00^{d}	2.33 ± 0.58^{e}	0.000
Day 21	71.33 ± 1.53^{a}	42.33 ± 15.04^{b}	24.00 ± 1.00^{c}	81.00 ± 1.00^{d}	0.33 ± 0.53^{e}	0.000

Day 7 = a was significantly different from b, c, d and e. Day 14= a was significantly different from b, c, d and e. Day 21 = a was significantly different from b, c, d and e

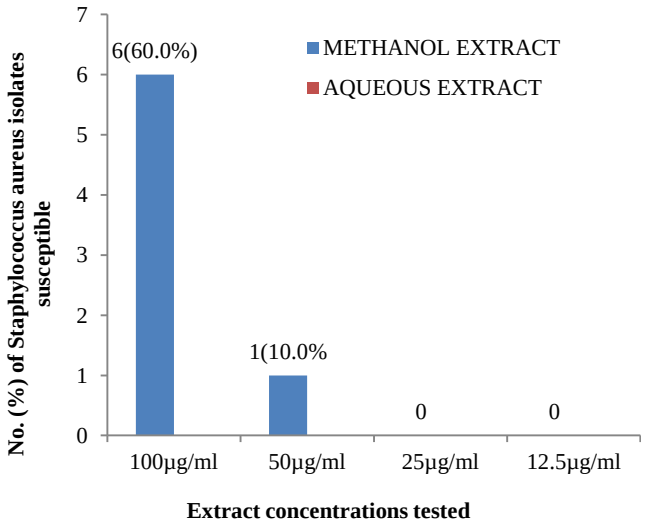

Figure 1: Susceptibility pattern of *Staphyloccocus aureus* isolates in Methanol and aqueous extract of *Lantana camara* leaf

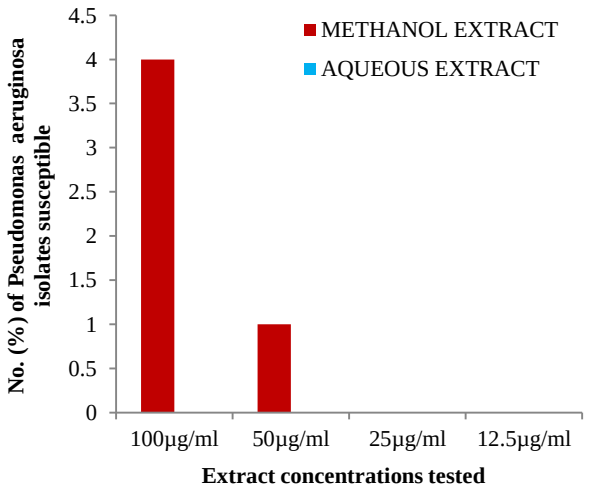

Figure 2: Susceptibility pattern of *Pseudomonas aeruginosa* isolates to methanol and aqueous extract of *Lantana camara*leaf

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Table 3: Mean wound contractions on Wistar rats inoculated with *Staphylococcus aureus*

Days	100 µg/mL (n=3)	50µg/mL (n=3)	25µg/mL (n=3)	Ofloxacin (100µg/mL) (n=3)	No treatment. (n=3)	P-Value
Day 7	40.67 ± 1.15^{a}	31.00 ± 1.00^{b}	11.00 ± 1.00^{c}	44.67 ± 58^{d}	4.67 ± 0.58^{e}	0.000
Day 14	60.33 ± 0.58^{a}	40.33 ± 0.58^{b}	9.67 ± 0.58^{a}	64.33 ± 1.15^{d}	4.33 ± 1.15^{e}	0.000
Day 21	74.33 ± 1.15^{a}	54.00 ± 1.00^{b}	15.00 ± 0.00^{c}	70.33 ± 0.58^{d}	9.07 ± 0.58^{e}	0.00

Day 7 = a was significantly different from b, c, d and e. Day 14= a was significantly different from b, c, d and e. Day 21 = a was significantly different from b, c, d and e

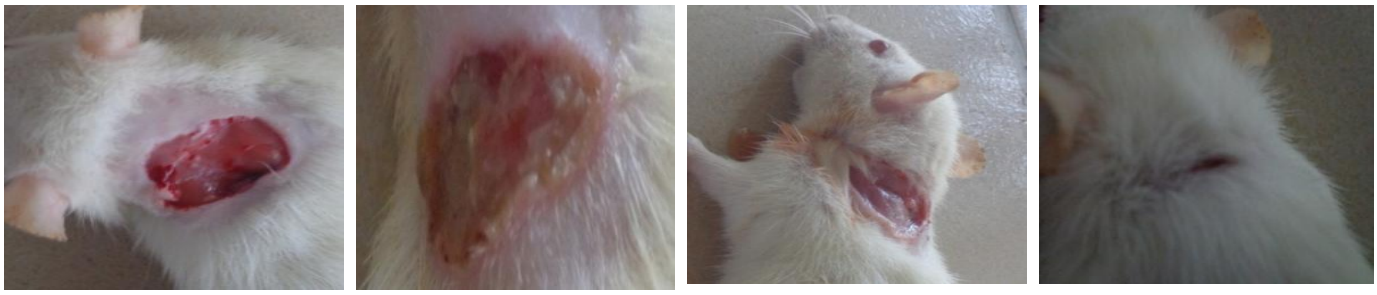

Plate 2: Fresh incision wound on rat.PLATE 3: Wound inoculated with *Pseudomonas aeruginosa* and untreated. PLATE 4: Wound infected with *P. aeruginosa* and treated with extract. PLATE 5: Wound completely healed

Good antimicrobial use is necessary for effective wound management.*Lantana camara*has therapeutic potential due to the presence of bioactive compounds such as flavones, flavonoids, anthocyanins, cumarins, lignans, catechins, alkaloids, tannin, saponins, triterpenoids.[22] Although these compounds were not investigated in this study, *Lantana camara*leaf extract showed antibacterial activity. The wound healing effect of *Lantana camara*leaf extract in this study was directly proportional to the concentration of the leaf extract. The mean contraction of the wounds were higher with higher concentrations of the extract while litle or no contraction occurred with the 25 mg/mL concentration and untreated wounds. This showed that wound treatment with the extract may be dose dependent.

The extract activity on wounds was compared with the activity of commonly used antimicrobial agents. The 100 µg/mL concentration of the leaf extract on wounds inoculated with *Staphylococcus aureus* and *Pseudomonas aeruginosa* resulted in mean wound contraction of 74.33 ± 1.15 and 71.00 ± 1.73 which are comparable to the 70.33 ± 0.58 and 81.00 ± 1.00 contraction produced by ofloxacin.

This revealed that *L. camara*leaf extract could be used as an alternative to ofloxacin in the treatment of these multidrug resistant bacterial wound infections. The leaf extract was more effective against *Staphylococcus aureus* infected wounds with mean wound contraction of 74.33 ± 1.15 than the 70.33 ± 0.58 mean wound contraction by ofloxacin on day 21. Our findings is in agreement with the work of Abdulla *et al.*[21] in Malaysia who reported that topical application of *L. camara*extracts had wound healing effect on rats.

The skin sections of the wounds treated with 100 mg/mL concentration of extract, showed damage tissue repair. There was fibro-collagen formation in the dermis with mild inflammatory cells. There was complete absence of thickening of the outer layer of the skin and the presence of fibrosis.

The skin sections of the wounds treated with 100 µg/mL of ofloxacin (positive control), showed stratified squamous epithelial cells with intact basement displaying mild hyperkeratosis. There were prominent pilosebaceous apparatus consisting of hair follicle and sebaceous glands. The dermis was fibrogenous with mild inflammatory infiltrates indicating damage tissues repairs by antimicrobials tested.

The common feature of the skin sections treated with 50 µg/mL concentration of the extract is marked cellular oedema and sparse inflammatory infiltrates within the reticular dermis.

On wounds treated with 25 **µ**g/mL concentration of leaf extract, the epidermis consists of stratified squamous epithelial cells with an intact basement displaying abnormal thickening of the outer layer of the skin. There was little reduction of inflammatory cells.

On the wounds left untreated, there were intense tissue reaction with destruction of the skin adnexae structures and abscess formation. There was mixed inflammatory cellular infiltrates composed mainly of mononuclear cells. Our findings are in agreement with the work of Levinson *et al.*[23]who reported changes in fibroblast- populated collagen and wound contractions.

Conclusion

This study revealed that methanol extract of *Lantana camara montevidensis* has broad spectrum antimicrobial activity on wound isolates. The different concentrations of *Lantana camara* leaf extract have different spectra of antibacterial activity. The leaf extract had topical healing effect on wounds as indicated by the mean wound contraction on the Wistar rats. Histologically, there was damaged tissue repair indicated by the presence of fibrocollagen formation with mild inflammatory cells. Therefore, *Lantana camara* montevidensis crude extract may be used for bacterial wound management.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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