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Antimicrobial potentials of *Lantana camara montevidensis* leaf extract on wounds infected with *Candida* isolates

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Abstract

The use of medicinal plants for therapeutic purposes is a secular tradition in different cultures. The emergence of antimicrobial resistance among microorganisms calls for alternative sources. Plants having antimicrobial activity against multidrug-resistant fungi may be considered good assets. In this study, we investigated the effect of different concentrations of *Lantana camara* leaf extract against *Candida* isolates from infected wounds *in vitro* and *in vivo* using animal models. Aqueous and methanol extraction was done using Soxhlet apparatus. *Candida albicans* isolates associated with wound infections were used for the study. Antifungal susceptibility testing was done using the E-Test strips. Male Wistar rats were used for the study. The rats were anesthetized before incision wounds were made. The rats were treated with 100mg/mL, 50mg/mL and 25mg/mL concentration of extract topically. The skin tissues of the sacrificed rats were obtained for histological examination using Haematoxylin and eosin technique. The susceptibility rate of the *Candida* isolates ranged from (0.0% - 40.0%). Rats treated with 100mg/mL methanol extract had best mean wound contractions of 70.3±0.58 with damaged tissue repair. Methanol extract of *Lantana camara* leaf had antimicrobial activity and topical healing effect on *Candida* infected wounds. It could be used as an alternative for *Candida* wound management.

Keywords: Antifungal activity, Leaf extract, Animal studies, Fungi, Wound healing

Introduction

Medicinal plant materials and herbal remedies derived from them represent a substantial portion of the global medicinal market. There is an increased focus in the development of drugs of herbs origin since there are good sources of active chemotherapeutic agents in treating different kinds of infectious diseases. Many communities in Nigeria and other African countries use plants to treat various infections, including wounds (Kirimuhuzya *et al*., 2009; Sharma *et al*., 2021). The most frequent use of herbs occurs in developing Nations, due to the high costs required in the manufacturing of modern medicines. About 90% of people living in developing countries resort to the use of natural herbs because they are cheap, affordable and effective alternatives. The developed nations have begun to take a look at herbal medicines for its potential in chemotherapy and health care (Ross, 1999). The World Health Organization (WHO) has reported that about 80% of people globally, use herbs as their main source of health care (WHO, 2002).

Lantana camara belong to the family *Verbanaceae*. It has more than 600 varieties and is a native terrestrial weed of South and Central American origin (Tiwari *et* al., 2022). It is now found in African nations even the arid zones. It is common in Kenya, Nigeria, Tanzania and Uganda. Its growth hinders other biodiversity because of its invasive nature. Other uses of *L. camara* have been reported, these include: making hedges, firewood, mulch, nematicides and insecticides (Bhagwat *et al*., 2012).

Traditional system of medicine is an unavoidable global discuss even when modern medicine has been available in developed nations, the use of herbs in treatment of diseases have usually gain popularity in cultural and historical settings. In Nigeria, the Efik/Ibibio people in South-southern region call the *Lantana camara* plant "Lantana lantana", the Igbos call it "Anya nnunu ? , the Yoruba people "Elepo and Ewonadele ?and the Hausas call it "Kimbama-Halba" (Sofowora, 1996; Abayomi *et al*., 2013). Other common names of *L. camara* include: wild-sage, red-sage, white-sage in the Caribbean, big-sage in Malaysia, korsu wiri or korsoe wiwiri in Suriname and South America, tick berry in South Africa (Nayak *et al*., 2009).

Problems of surgical wounds

Surgical site infections also known as surgical wounds are dreaded complications of surgery. The National Nosocomial Infections Surveillance (NNIS) system set by the Centers for Disease Control and Prevention (CDC) ranked surgical wounds third among all reported cases of inpatient nosocomial infections. Surgical wounds account for about 16% of nosocomial infections in all hospitalized patients and 38% of all surgical patients (*Quentin et al., 1995; Ogba et al., 2014a).*

Surgical wounds remain a problem in surgery, despite significant advances in surgical techniques, modern technologies in the operating room, and preemptive measures such as perioperative intravenous antibiotics and preoperative skin antisepsis. It increases a patient's risk of morbidity and mortality and can have serious economic consequences (Anderson *et al*., 2015; Lee *et al*., 2006). The annual incidence of surgical wounds are between 31,000 and 35,000 (Thakore *et al*., 2015). Most surgical incisions heal by primary intention where the wound edges are apposed with sutures, clips or glue. However, some heal by secondary intention where the wound is left open and heals by formation of granulation tissue (Graf *et al*., 2011).

Wound infections are important because they can slow down the healing process, lead to wound breakdown, prolong hospital stay and increase in the cost of treatment. In developing countries, traumatic and surgical site infections are reasons for high morbidity and mortality rates (Onyekwelu *et al*., 2017; Greene, 2012). New antimicrobial agents are being developed in response to the emergence of resistance to existing antibiotics and antifungal agents. Vegetal plants with antimicrobial activity could be viable alternatives. *Lantana camara* leaves are easily accessible at low or no cost where species are found.

Antimicrobial plant sources and wound healing

Globally, the use of medicinal plants in acute and chronic wounds management in most traditional medicine practices is a common occurrence. In view of this, many plants in the tropical and subtropical regions of the world have been screened for wound-healing abilities (Ogba *et al*., 2014b). Despite the growing menace of antibiotic resistance, plants are promising sources of antibiotics with possible activity on multidrug-resistant microorganisms (Agyare *et al*., 2009). The potentials of plant extract as alternative sources of antibiotics against wound pathogens have been under-explored, especially in developing countries. Some medicinal plants have not been screened in the search for newer, efficacious, and cost-effective wound-healing properties.

In Nigeria, Udegbunam and Colleagues (2014) assessed the wound healing and antibacterial properties of Pupalia lappacea Juss. In Ghana, Boakye *et al.* (2018) investigated the invivo wound-healing activity of aqueous aerial part extract of a medicinal plant using Phyllanthus muellerianus. Also, Agyare and Colleagues (2009) evaluated the antimicrobial and wound healing potential of two plants; Justicia flava and Lannea welwitschii. It is therefore important to explore more plants that are locally available and of low cost, as potential sources of antifungal agents against wounds infected with fungal pathogens to contribute to effective management of wound infections.

Few studies on wound healing activity of *Lantana camara* have been reported. Ogba *et al.* (2021) reported that *Lantana camara* leaves have healing properties on bacterial wound infections. Farah *et al.* (2018) in India reported that *Lantana camara* leaves have healing

properties on burns. Nayak *et al.* (2009) also studied the healing activity of the leaf extract of *L. camara* in excision wound on rats but measured the wound healing efficacy using biochemical parameters. This study aimed to determine the effect of different concentrations of *Lantana camara* leaf extract against *Candida* isolates from infected wounds *in vitro* and *in vivo*.

Materials and Methods

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

Plant collection and identification

Lantana camara leaves *were* plucked from hedges and gardens in Calabar municipality, Cross River State. Only plants judged as mature were plucked. The collection was done during the rainy season when the plants florish better. The Plant leaves that appeared to be infected were discarded. This is indicated by white patches, yellowing or browning of the leaves (Farah *et al*., 2018). The matured leaves with fresh shoot and flowers with no sign of external damage were identified by a Botanist, A Professor in the Department of Biology, Faculty of Biological Sciences, Cross River University of Technology (CRUITECH) with Voucher number: Bot/Herb/Ucc/062.

***Lantana camara* leaf extraction**

Extraction by Soxhlet method was done in the Department of Pharmacology, University of Calabar, and standardized accordingly. Five hundred grams of leaves were shade-dried, pulverized and packed. Twenty-five grams of the dried powder of leaf 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 10 grams of extract was collected (Dash *et al*., 2001).

Test organisms

Known *Candida albicans* isolates from wound infections were obtained from the Microbiology/Parasitology Laboratory, University of Calabar Teaching Hospital for invitro and in vivo analysis. The isolates were maintained as stock in Sabouraud dextrose agar (SDA) slants. Each isolate was sub cultured on SDA at 37^0C for 24 hours before use (Badakhshan *et al*., 2009).

Antifungal agents

All the antifungal discs were procured from commercial sources. Fluconazole (FCZ) (Lot No: 80292115) was obtained from Neimeth Pharmaceuticals, Nigeria. Itraconazole (ITZ) (Lot No: 14001) was obtained from Hanmi Pharmaceuticals, Korea. Ketoconazole (KTZ) (Batch No: BA067002), Clotrimazole (Batch No: 160001) and Nystatin (Lot No: 873292118) were obtained from Torrent Pharmaceuticals, India.

Antifungal susceptibility testing

The *Candida albicans* isolates were subjected to antifungal susceptibility testing according to the CLSI document M100-S23 (Jalalpure *et al*., 2008). The antifungal agents tested were: Fluconazole, Clotrimazole, Nystatin and Itraconazole.

Susceptibility testing of *Lantana camara* leaf extract

Different concentrations of the plant extract were incorporated onto 6mm diameter Whatman filter paper number one discs. The discs were dried at 37°C and controlled before use. The different disc concentrations were 100µg, 50µg, 25µg and 12.5µg. The isolates were tested by Kirby-Bauer (disc diffusion) method to determine the susceptibility of isolates to the extract.

Determination of Minimum Inhibitory Concentration (MIC)

The minimum inhibitory concentration (MIC) of the extract was determined. A rack of sterile 20mL tubes were set up, eleven tubes for each isolate. The 11 tubes were labeled 10µg/mL, 5µg/mL, 2.5µg/mL, 1.25µg/mL, 0.625µg/mL, 0.312µg/mL, 0.156µg/mL, 0.0781µg/mL and 0.0390µg/mL respectively. Tubes 10 and 11 were the negative and positive control tubes. The negative control tube contained equal volume of the extract and peptone water with no inoculum while the positive control tube was extract free with peptone water and inoculum.

The Extract powder (0.1g) was dissolved in 10mL of sterile distilled water. The stock was equivalent to 100µg/mL. One in ten-fold dilution was performed from the stock solution in peptone water to give 10µg/mL. Then 4mL of peptone water was dispensed to tubes 2 to 10, 8mL of the 10µg/mL extract was dispensed into tube 1 and a serial dilution of 4mL from tube 1 to tube 2 through tube ten was done. This was repeated for the other 22 tubes with the other two clinical isolates. The dilution was carried out with sterile pipettes.

The tubes containing known concentrations of various extracts as well as extract-free controls were inoculated with 10µl of 0.5 McFarland standard adjusted suspensions of inoculum by the use of an automatic pipette. A loopful of the inoculum suspension was streaked onto Nutrient agar and Sabouraud dextrose agar plates to check the purity and viability. All cultures were incubated for 48 hours at 37°C or until good growth was apparent in the extract-free control. The tubes with the lowest concentration of extract with the best clearance were regarded as the MIC (Ogba *et al*., 2013).

Minimum Fungicidal Concentration (MFC)

Fungicidal concentration was determined by sub-culturing the broth of the tubes after the MIC tube along with the content of the MIC tube on separate culture plates. All the inoculated plates were incubated at 37°C for 24hrs, after which they were observed for growth. The Minimum fungicidal concentration was the plate with the lowest concentration of the extract without growth (Ogba *et al*., 2013).

Extract preparation for wounds

The following concentrations were prepared for topical treatment of the incision wounds on the Wister rats. One gram of the methanol *Lantana camara* leaf extract was dissolved in 10mls of distilled water. This is equivalent to 100mg/mL of the extract. The target concentrations of the extract for the topical applications were 100mg/mL (high dose), 50mg/mL (medium dose) and 25mg/mL (low dose). One in 2 dilution of this stock in distilled water contained 50mg/mL of the extract. The desired concentration for each group was applied as 0.1mL topically. The wounds were monitored for 21 days before the animals were sacrificed and skin sections obtained for histopathology testing. The antibiotics used as controls were also diluted to the corresponding concentrations 100mg/mL (high dose), 50mg/mL (medium dose) and 25mg/mL (low dose), before application (CLSI, 2012).

Preparation of yeasts inoculum

Brain Heart Infusion Broth (BHIB 3.8%) was used for the yeasts 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 (CLSI, 2012).

Experimental animals

Fifteen 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 methanol extract of *L. camara* leaf for 21 days on wounds infected by *Candida albicans*. The animals were divided into five groups of three 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) (Barreto *et al*., 2010).

The animals were given wound incisions and inoculated with *Candida albicans*. Three rats each were treated with different concentrations (100mg/mL, 50mg/mL and 25mg/mL) of the *L. camara montevidensis* extract topically. The control groups were treated with 100mg/mL of fluconazole while the fifth group (negative control) was left untreated.

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

Day1

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 minutes, 0.5ml of the inoculum of *Candida albicans* were introduced into each wound incision (Sofowora, 1996; Barreto *et al*., 2010).

Day 2

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

Day3 – 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 (Barreto *et al*., 2010).

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.

% Wound contraction = Initial wound size – specific day wound size x 100

Initial wound size

(Guo-Bing *et al.,* 2014)

Data analysis

Data obtained from the study was analyzed using Epi Info 2010 (CDC, Atlanta, 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

Table 1 shows the susceptibility pattern of the *Candida* isolates to commonly used antifungal agents. *Candida* isolates were most susceptible to fluconazole 4/10(40%), followed by Nystatin 2/10(20.0%), but all the isolates were resistant to itraconazole and clotrimazole.

Table 2 shows the susceptibility pattern of *Candida* isolates to methanol extract of *Lantana camara* leaf. The isolates were most susceptible (40.0%) to the 100µg/mL extract. All the isolates were resistant to the 25µg/mL and 12.5µg/mL extracts respectively.

Candida isolates were not susceptible to aqueous extract of *Lantana camara* leaf. The isolates were all resistant to the different concentrations (100g/mL, 50g/mL, 25g/mL and 12.5g/mL) of the aqueous extract.

Table 1: Susceptibility pattern of *Candida* isolates to antibiotics

Clinical isolates	No. tested	Antibiotics tested			
		No. (%) of isolates susceptible			
		Flu	Itr	Cltr	Nys
Candida isolates	10	4(40.0)	0(0.0)	0(0.0)	2(20.0)

Key:
FLU – Fluconazole
ITR – Itraconazole
CLTR – Clotrimazole
NYS - Nystatin

Table 2: Susceptibility pattern of *Candida* isolates to methanol extract of *Lantana camara* leaf

Clinical isolates	No. tested	Extract concentrations tested/ No . (%) of isolates susceptible			
		100 µg	50 µg	25 µg	12.5 µg
Candida isolates	10	4(40.0)	1(10.0)	Nil	Nil

Table 3 shows the effect of treatments and wound contraction on the Wistar rats inoculated with *C. albicans*. The treatment groups with 100mg/mL extracts on the various isolates showed significant wound healing at 75.0%, 70.0% and 55.0% wound contraction respectively. The positive control rats showed good healing while the negative control rats exhibited no healing at 10.0%, 0.0% and 0.0% respectively. Table 4 shows the mean wounds contractions on Wistar rats inoculated with *C. albicans*. There was a statistically significant difference between the wound contractions on rats treated with 100mg/mL of ethanol extract and the other extract concentrations.

Figure 1 shows the longitudinal section of the Wistar rat wounds infected with *Candida albicans* and treated with different concentrations of extract. Figure 2 shows the longitudinal section of the Wistar rat skin infected with *Candida albicans* left untreated and treated with 100mg/mL Fluconazole.

Table 3: Effect of treatments and wound contraction on the Wistar rats

Rat groups	Treatments	Percentage of wound contraction in days		
		Day 7	Day 14	Day 21
		Animals inoculated with *Candida* species		
Rat 1-3	100mg/mL	25.0	35.0	55.0
		25.0	35.0	54.0
		24.0	33.0	53.0
Rat 4-6	50mg/mL	10.0	25.0	35.0
		9.0	24.0	35.0
		10.0	25.0	33.0
Rat 7-9	25mg/mL	5.0	0.0	0.0
		5.0	0.0	0.0
		4.0	0.0	0.0
Rat 10-12	100mg/mL	45.0	60.0	70.0
	Fluconazole	43.0	61.0	70.0
		45.0	60.0	71.0
Rat 13-15	No treatment	4.0	6.0	8.0
		4.0	6.0	0.0
		3.0	5.0	0.0

Table 4: Mean wounds contractions on Wistar rats inoculated with *Candida* species.

Days	100mg/mL (n=3)	50mg/mL (n=3)	25mg/mL (n=3)	fluconazole (100mg/mL). (n=3)	No treatment. (n=3)	p-value
Day 7	24.67 ± 0.58^{a}	9.67 ± 0.58^{b}	4.67 ± 0.58^{c}	44.33 ± 1.15^{d}	4.00 ± 0.00^{e}	0.000
Day 14	$35.0.00\pm0.00^{a}$	24.67 ± 0.58^{b}	0.00 ± 0.00^{c}	60.33 ± 1.58^{d}	5.67 ± 0.58^{e}	0.000
Day 21	54.00 ± 1.00^{a}	34.33 ± 1.15^{b}	0.00 ± 0.00^{c}	0.00 ± 0.00^{d}	0.00 ± 0.00^{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

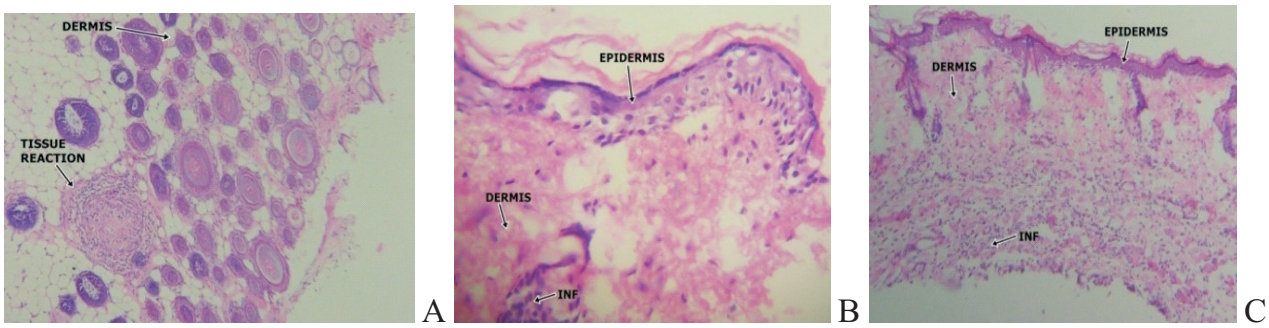

Figure 1: Longitudinal section of the Wistar rat skin infected with *Candida* isolates and treated with (A) 100mg/mL *L. camara* extract
(B) 50mg/mL *L. camara* extract
(C) 25mg/mL *L. camara* leaf extract (x100)

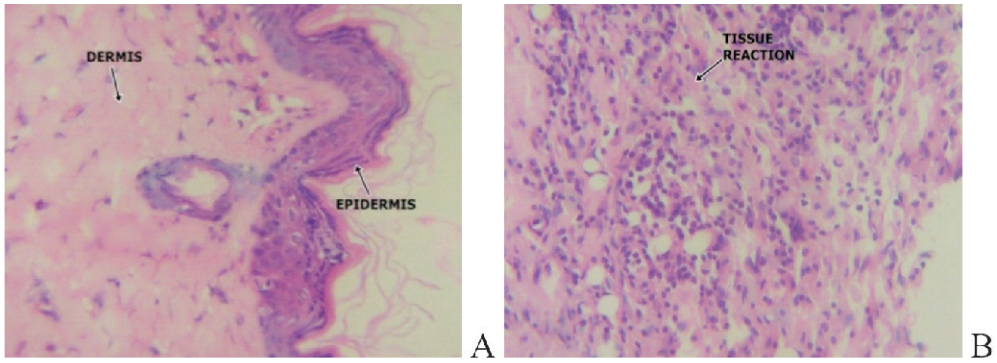

Figure 2: Longitudinal section of the Wistar rat skin infected with *Candida albicans*
A. Treated with 100mg/mL Fluconazole
B. Untreated infected skin (x100)

Discussion

In this study, the antimicrobial activity of *Lantana camara montevidensis* leaf extract on selected *Candida albicans* isolates associated with wound infections was tested *in vitro* and *in vivo*. *Lantana camara montevidensis* methanol leaf extract was tested *in vitro* on wound isolates and *in vivo* on induced wounds on albino Wistar rats. The activity of *Lantana camara* leaf extracts varied with the solvent of concentration. The activity of alcohol extracts over water extracts have been reported in previous studies (Puratchikody *et al*., 2006).

This study revealed that the crude extract of *Lantana camara* leaf have antimicrobial potentials against *C. albicans*. The activity peaked at a concentration of 100µg/ml with 40.0% susceptibility rate. There was no activity at 25µg and 12.5µg respectively. This depicts that higher concentrations of the crude extract is required for effective treatment of *Candida* infections. Our findings is in agreement with the study of Mudasir *et al*. (2017) who reported that leaf extracts at higher concentrations inhibited the growth of fungal isolates including *Candida* species.

Fluconazole has been reported as the most frequently used anticandidal agent globally. The most effective antifungal in this study was fluconazole (Flu), this is consistent with the report of Tang and Colleagues (2008) and Adhikary and Joshi (2011) where the isolates displayed marked susceptibility to fluconazole.

Lantana camara has therapeutic potential due to the presence of bioactive compounds such as flavones, flavonoids, anthocyanins, cumarins, lignans, catechins, alkaloids, tannin, saponins, triterpenoids (Scorzoni *et al*., 2017). Although these compounds were not investigated in this study, *Lantana camara* leaf extract showed antifungal 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 25mg/mL concentration and untreated wounds. This showed that wound treatment with the extract may be dose dependent.

The skin sections of the wounds treated with 100mg/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 common feature of the skin sections treated with 50mg/mL concentration of the extract is marked cellular oedema and sparse inflammatory infiltrates within the reticular dermis.

On wounds treated with 25mg/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 finding is in agreement with the work of Levinson *et al.* (2004) who reported changes in fibroblast populated collagen and wound contractions.

Conclusion

Methanol extract of *Lantana camara montevidensis* had higher activity on the *Candida albicans* in vivo and invitro. The leaf extract had topical healing effect on the induced wounds as indicated by the mean wound contraction on the Wistar rats. Histologically, there was damaged tissue repair indicated by the presence of fibro collagen formation with mild inflammatory cells.

Therefore, *Lantana camara montevidensis* crude extract may be used for yeasts infected wound management.

Authors' contributions

OMO conceived the study. SNE, OMO and SA contributed to the design of the study. OMO and SNE performed the laboratory studies. SNE, GPB and OMO analyzed the data and drafted the manuscript. OMO is the guarantor of the paper. All authors read and approved the final version.

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