Original Research Article

**In vitro and In vivo Antibacterial and Anti-inflammatory Properties of Linalool**

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**Abstract**

The present study was planned to determine in vitro and in vivo antibacterial and anti-inflammatory properties of Linalool. In vitro antibacterial activity of Linalool was determined by micro broth dilution technique and MICs were observed as 1.25, 1.25, 1.25, 0.63, 1.25, 0.63 and 1.25 mg/ml against *Staphylococcus aureus*, *Streptococcus pyogenus*, *Bacillus subtillis*, *Escherichia coli*, *Salmonella typhimurium*, *Pseudomonas aeruginosa* and *Proteus mirabilis*, respectively. In vivo antibacterial efficacy of Linalool was determined in neutropenic rat thigh infection model and significant antibacterial efficacy was observed as compared to growth control with bacterial colony count $4.07 \pm 0.05 \log_{10}$ cfu/ml. In vitro anti-inflammatory activity was tested for their ability to inhibit COX-2 enzyme by measuring PGE$_2$ level and determination of NO production in LPS treated RAW264.7 macrophage cells. At all concentrations of Linalool (10, 50 and 100 µM) found to have significant inhibition of NO and PGE$_2$ production compared with LPS control group. In vivo anti-inflammatory activity of Linalool (100 mg/kg) was assessed using the carrageenan-induced rat paw edema model at different time intervals following intramuscular injection and observed significant percent inhibition of edema volume compared with carrageenan control group.

**Keywords**

Linalool, Antibacterial, Anti-inflammatory, Carrageenan, Lipopolysaccharide, Rat

**Article Info**

Accepted: 12 August 2020
Available Online: 10 September 2020

**Introduction**

Since ancient era, Indian people have intellectual knowledge of traditional medicine and were used to treat many acute and chronic diseases in human as well as in animal being. Natural sources like plants, animals, microbes are also of great interest in new drug discovery. Furthermore, India has wide diversity in nature which is beneficial to identify newer molecules as therapeutic agent. Phytochemicals like terpenes and terpenoids are used as flavoring agent and play a diverse role in the field of drugs and cosmetics (Perveen, 2018). Linalool is an acyclic monoterpenic tertiary alcohol and derived from plants mainly Lamiaceae, Lauraceae and Rutaceae families. Linalool is known to reveal various pharmacological activities such as antimicrobial, anti-inflammatory,
antioxidant and anticancer properties (Kamatou and Viljoen, 2008). Terpenoids are also found in spices and condiments which we are using in our routine life and can be used in primary healthcare. Looking to above facts, present study was planned to evaluate in vitro and in vivo antibacterial and anti-inflammatory activities of Linalool.

**Materials and Methods**

**Animals**

This study was conducted on female albino wistar rats weighing 305 ± 2.60 grams and 353 ± 4.81 grams for in vivo anti-inflammatory and antibacterial protocol, respectively. The experimental protocol was approved by Institutional Animal Ethics Committee (IAEC) of Veterinary College, NAU, Navsari with permission number 057-VCN-VPT-2018.

**Reagents**

Linalool (97%), Lambda (λ) carrageenan, Nω-Nitro-L-arginine methyl ester hydrochloride (NAME), Dulbecco’s Modified Eagle’s Medium – high glucose (DMEM), Meloxicam, Lipopolysaccharide (LPS), Cyclophosphamide, Iodonitrotetrazolium chloride (INT) and 3-(4,5-dimethylthiazol-2yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) were purchased from Sigma-Aldrich, St. Louis, USA.

Indomethacin was obtained from Calbiochem. Dimethylsulfoxide (DMSO) and Sodium nitrite were purchased from Merck Specialties Private Limited, Mumbai. Chloramphenicol, Celecoxib, Sulfanilamide, N-(1-Naphthyl) ethylenediaminedihydrochloride (NEDD), Eosin Methylene Blue (EMB) agar, Fetal bovine serum, Brain heart infusion (BHI) broth and antibiotic antimycotic solution 100X liquid were purchased from Himedia Laboratories Private Limited, Mumbai. Typed bacterial cultures were purchased from National Collection of Industrial Microorganisms (NCIM), Pune and murine macrophage cell line RAW 264.7 was purchased from National Centre for Cell Science (NCCS), Pune. Ethanol was used from store of Veterinary College, NAU, Navsari after triple distillation. HPLC grade de-ionized water was used in all in vitro and in vivo procedures.

Prostaglandin E2 express ELISA kit (Item No. 500141) was purchased from Cayman Chemical Company, Ann Arbor, MI USA.

**In vitro antibacterial effect**

Linalool stock (40 mg/ml) was prepared in 3% Tween-20. Chloramphenicol stock (250 μg/ml) was prepared in sterile water to use as positive control. Bacterial cultures were prepared to Mcfarland 0.5 standard equivalent to 1.5 x 10⁸ cfu/ml. Final dispensing inoculums were prepared in sterile test tubes by adding 2 ml bacterial suspension (1.5 x 10⁸ cfu/ml) of respective organisms into 198 ml of sterile broth. Final dispensing inoculums concentration was 1.5 x 10⁶ cfu/ml.

Minimum inhibitory concentrations (MICs) of Linalool were determined for different gram positive and gram negative organisms like Staphylococcus aureus (ATCC25923), Streptococcus pyogenus (ATCC8668), Bacillus subtilis (ATCC9372), Escherichia coli (ATCC25922), Salmonella typhimurium (ATCC23564), Pseudomonas aerugonosa (ATCC27853) and Proteus mirabilis (NCIM2241) by microbroth dilution technique (Wiegand et al., 2008; Modi et al., 2018). Iodonitrotetrazolium chloride (INT) dye was used to observe visual viability of bacteria. The assay was performed in triplicate.
In vivo antibacterial efficacy

In vivo antibacterial efficacy of Linalool was evaluated in neutropenic rat thigh infection model (Zhao et al., 2016). Neutropenic rat model was prepared by injecting cyclophosphamide intraperitoneally in rats on days 1 (150 mg/kg) and on day 4 (100 mg/kg). After confirmation of neutropenic condition, rats were infected with 0.2 ml bacterial suspension of *Escherichia coli* ATCC25922 (1.5 x 10^8 cfu/ml) in left thigh on same day. Linalool (100 mg/kg) which was prepared in DMSO was administered intramuscularly at total injectable volume of 200µl at 2 h and 8 h post infection in right thigh (Group-I). Group-II animals were treated with bacterial suspension (0.2 ml, IM) and Chloramphenicol (50 mg/kg, IM) (Positive Control), Group-III animals were treated with bacterial suspension (0.2 ml, IM) and DMSO (0.2 ml, IM) (Vehicle Control), Group-IV animals were treated with only bacterial suspension (0.2 ml, IM) (Growth Control). After 24 hours, 1 gram thigh muscle samples from infected site were collected following euthanasia under sterile condition. Suitable dilution of samples were inoculated on Eosin Methylene Blue (EMB) agar plates and incubated overnight at 37°C. Bacterial colonies were enumerated by colony counter and log_{10}cfu/gram was calculated.

In vitro anti-inflammatory effect

In vitro anti-inflammatory effect of Linalool was evaluated in murine macrophage cell line RAW 264.7 by measuring COX-2 enzyme inhibition via detection of PGE_2 concentration and by measuring NO production inhibition. Linalool (100 µM, 50 µM and 10 µM) was prepared in 0.008% ethanol in cell culture medium. Cells were grown in DMEM (Dulbecco’s Modified Eagle Medium) high glucose supplemented with 10% foetal bovine serum, 1% antibiotic antimycotic solution 100X. The cells were transferred in 12 well plate (1 x 10^6 cells per well) and incubated for 24 hours at 37°C and 5% CO_2 in humidified condition. The cells again washed and supplemented with 1600 µL fresh cell culture medium and 200 µL Linalool in different concentrations (100 µM, 50 µM and 10 µM) for NO production inhibition and PGE_2 inhibition assay. Positive control wells in NO production inhibition assay includes 1600 µL fresh cell culture medium and 200 µL Nω-Nitro-L-arginine methyl ester hydrochloride (NAME, 100 µM) and for PGE_2 inhibition assay positive control wells were dispensed with 1600 µL cell culture medium and 200 µL Celecoxib (100 µM). Vehicle control wells were dispensed with 1600 µL cell culture medium and 200 µL 0.008% ethanol and LPS control wells were dispensed with 1800 µL cell culture medium. Assay was performed in triplicate for test drugs and standards. All plates were incubated at 37°C and 5% CO_2 in humidified condition for 2 hours. Then 200 µL LPS (1 µg/ml) was added in all wells and again incubated at 37°C and 5% CO_2 in humidified condition for 24 hours. After incubation, supernatant was collected in sterile microcentrifuge tubes individually and centrifuged at 3000 rpm for 5 minutes. Supernatant was collected and divided in two parts: one was used to quantify COX-2 enzyme via measuring PGE_2 concentration using Prostaglandin E_2 express ELISA kit from Cayman Chemical Company, Ann Arbor, MI USA following procedure as recommended by the manufacturer (Barton et al., 2014) and another part was used to quantify nitrite accumulated in medium as an indicator of NO production using Griess reaction (Choi et al., 2018). Sodium nitrite standard calibration curve (1.56 µM to 50.0 µM) was prepared to validate the method of estimation and using correlation equation, concentration of NO was evaluated. Results were expressed as percent inhibition of NO and PGE_2 production in comparison to LPS control.
Cell viability

Cell viability was also carried out in test samples by MTT assay (Choi et al., 2018). After sample collection for assay, twenty µL of MTT solution (5 mg/ml) was added to each well, and the plates were incubated for 4 h at 37°C. The supernatants were then collected and the formed formazan crystals in each well were dissolved in 200 µL of dimethyl sulfoxide (DMSO) for 30 minutes at 37°C. The optical density at 570 nm was read in spectrophotometer. Cell viability percentage was calculated.

In vivo anti-inflammatory efficacy

The carrageenan-induced rat paw edema model was used with minor modification as described by (Suebsasana et al., 2009; Modi et al., 2019). Linalool (100 mg/kg) and Indomethacin (5 mg/kg) were prepared in DMSO. Experiment animals (n=24) were divided into 4 groups with 6 animals in each group. A mark on the left hind paw was made in each animal and initial volume was measured by immersing in the plethysmometer persplex tube. Group-I animals were kept as Carrageenan control. Group-II animals were given DMSO (Vehicle Control), Group-III animals were treated with Indomethacin (5 mg/kg IM) and Group-IV animals were treated with Linalool (100 mg/kg IM). Lambda carrageenan solution (1%) prepared in 0.9% normal saline and 100 µl was injected subcutaneously into sub plantar region of left hind paw. Half an hour before the carrageenan administration, test drug and positive control drug were injected via intramuscular route in respective animal groups. Oedema was measured in paw volume (ml) before carageenan administration and at 1, 2, 3, 4, 5 and 6 h after carrageenan administration and expressed as percent oedema formation in relation to initial paw volume before carrageenan injection for each animal. The paw volume data for test drug and positive control drug were analyzed and expressed as percent inhibition of oedema formation in comparison to carrageenan control group.

Statistical analysis

Data are expressed as Mean ± S.E. The data were analysed using one way ANOVA and significance level was checked at 1 per cent and 5 per cent by Duncan's New Multiple Range Test (DNMRT) using SPSS-20 software.

Results and Discussion

Antibacterial effect

Minimum inhibitory concentration of Linalool against Staphylococcus aureus, Streptococcus pyogenus, Bacillus subtilis, Escherichia coli, Salmonella typhimurium, Pseudomonas aerugonosaand Proteus mirabilis were observed as 1.25, 1.25, 1.25, 0.63, 1.25, 1.25 and 1.25 mg/ml (Table 1). Significant in vivo antibacterial efficacy of Linalool was observed using neutropenic rat thigh infection model with Escherichia coli colony count as 4.07 ± 0.05 Log10 cfu/ml (Table 2).

Anti-inflammatory Effect

In present study, percent inhibitions of NO production were measured as 37.47 ± 3.30 %, 55.51 ± 2.84 % and 63.07 ± 1.84 % and percent inhibition of PGE2 production observed as 93.31 ± 0.42 %, 94.34 ± 0.89 % and 94.35 ± 0.29 % at concentrations of 10, 50 and 100 µM, respectively with significant difference at all concentrations in comparison to LPS control (Table 3). Cell viability percentages of cells treated Linalool and other standards including LPS control were compared with blank control and found more
than 96% viability in all. In present in vivo experiment, percent increase in edema volume (8.36 ± 3.94%, 36.29 ± 4.86%, 35.22 ± 4.76%, 36.04 ± 4.32%, 36.88 ± 5.34% and 32.82 ± 4.88%) were significantly lower in comparison with carrageenan control group following administration of Linalool at 1, 2, 3, 4, 5, and 6 hours, respectively (Figure 1). In addition, following intramuscular administration of Linalool, significant percent increase in paw volume percent inhibitions were observed from 3 to 6 hours (Table 4).

Table 1 Minimum Inhibitory Concentrations of Linalool against various gram positive and gram negative organisms

| Organism                        | Linalool (mg/ml) | 1 | 2 | 3 | Mode |
|---------------------------------|-----------------|---|---|---|------|
| Staphylococcus aureus ATCC25923 | 1.25            | 1.25| 1.25| 1.25|
| Streptococcus pyogenes ATCC8668 | 1.25            | 0.63| 1.25| 1.25|
| Bacillus subtilis ATCC9372      | 1.25            | 1.25| 1.25| 1.25|
| Escherichia coli ATCC25922      | 0.63            | 0.63| 0.63| 0.63|
| Salmonella typhimurium ATCC23564  | 1.25             | 1.25| 1.25| 1.25|
| Pseudomonas aeruginosa ATCC27853 | 0.63            | 1.25| 0.63| 0.63|
| Proteus mirabilis NCIM2241      | 1.25            | 1.25| 1.25| 1.25|

Table 2 Log10 cfu/ml of Escherichia coli (1.5x10^8 cfu/ml) in infected thigh samples of rats treated with drugs including control groups (n=6)

| Treatment groups   | Bacterial colony count (Log10 cfu/ml) | Mean ± S.E. |
|--------------------|--------------------------------------|-------------|
|                    | Rat number                           |             |
|                    | R1        | R2        | R3        | R4        | R5        | R6        |          |
| Growth control     | 5.40      | 5.28      | 5.44      | 5.20      | 5.32      | 5.42      | 5.35 ± 0.03^a |
| Vehicle control    | 5.44      | 5.23      | 5.39      | 5.28      | 5.36      | 5.33      | 5.34 ± 0.03^a |
| Chloramphenicol    | 4.08      | 3.90      | 4.18      | 3.95      | 4.15      | 4.00      | 4.05 ± 0.04^b |
| Linalool           | 4.18      | 3.90      | 4.11      | 4.04      | 4.20      | 3.90      | 4.07 ± 0.05^b |

Means bearing different superscripts between treatment groups differ significantly (p<0.01)

Table 3 In vitro percentage inhibition of NO and PGE2 production in LPS induced RAW 264.7 cells treated with different concentrations of Linalool

| Treatment group   | Percent inhibition (%)± S.E. of NO production | Percent inhibition (%)± S.E. of PGE2 production |
|-------------------|-------------------------------------------------|-----------------------------------------------|
| Positive Control  | 75.72 ± 2.52^b                                  | 99.72 ± 0.04^b                               |
| Vehicle Control   | 6.52 ± 1.50^a                                   | 3.59 ± 1.33^a                                |
| Linalool (10 μM)  | 37.47 ± 3.30^c                                  | 93.31 ± 0.42^c                               |
| Linalool (50 μM)  | 55.51 ± 2.84^d                                  | 94.34 ± 0.89^c                               |
| Linalool (100 μM) | 63.07 ± 1.84^d                                  | 94.35 ± 0.29^c                               |

Means bearing different superscripts between treatment groups differ significantly (p<0.01)
Table 4 Percent increase (%) in paw volumes (Mean ± S.E.) of carrageenan induced inflammation in rats treated with drugs compared with 0 hour (n=6)

| Group      | 1 Hour      | 2 Hours     | 3 Hours     | 4 Hours     | 5 Hours     | 6 Hours     |
|------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Carrageenan| 48.18±2.62abA | 60.21±2.58B | 68.68±3.38bB | 80.57±3.04cC | 88.01±2.82cC | 103.39±3.27dD |
| Vehicle    | 34.86±4.25abA | (27.65±8.83abA) | 58.83±2.56cC | (14.34±3.73dC) | 70.39±4.22dD | (12.63±5.24dD) | 75.42±4.00dD | (14.31±4.55dD) | 90.60±2.89dE | (12.37±2.80dE) |
| Indomethacin| 33.09±7.39bA | (31.32±15.3bA) | 9.49±4.35bB | (86.18±6.33bB) | 36.42±9.32bB | (54.80±11.57bB) | 44.97±8.69bA | (48.90±9.88bA) | 47.00±8.31bA | (54.54±8.03bA) |
| Linalool   | 8.36±3.94cA | (82.65±8.18cA) | 35.22±4.76bB | (48.72±6.94bB) | 36.04±4.32bB | (55.27±5.36bB) | 36.88±5.34bB | (58.10±6.07bB) | 32.82±4.88bB | (68.26±4.72bB) |

Figures in parenthesis shows percent inhibition (%)± S.E. compared with carrageenan control Means bearing different superscripts in small letters between treatment groups and in capital letters within groups differ significantly (p<0.01)

Figure 1 Percent increase (%) in paw volumes (Mean ± S.E.) of carrageenan induced inflammation in rats treated with drugs compared with 0 hour (n=6)

Results of present in vitro antibacterial study are in agreement with MICs of Linalool were observed by other researchers as 1.024mg/ml against Staphylococcus aureus and Pseudomonas aeruginosa (Silva et al., 2015) and against Escherichia coli and Staphylococcus aureus as 0.77 mg/ml and 1.54 mg/ml, respectively (Jabir et al., 2018). In contrast to present study, lower MICs were observed as 5.0, 4.0, 6.0, 5.0, 7.0 and 6.0 μg/ml against Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Salmonella typhimurium, Pseudomonas aeruginosa and Proteus mirabilis,
respectively (Sokovic et al., 2010). Similarly, Dumanet et al., (2010) also observed lower MICs as 0.7, 0.9 and 0.7 μg/ml against Pseudomonas aerugonosa, Escherichia coli and Staphylococcus aureus, respectively. Furthermore, in present study statistically significant in vivo antibacterial efficacy of Linalool was observed as compared to growth control in neutropenic rat thigh infection (Escherichia coli) model with bacterial colony count 4.07 ± 0.05 Log_{10} cfu/ml which was in agreement with present in vitro observations.

Statistically significant and dose dependent percent inhibitions of NO production was observed with Linalool (10, 50 and 100 μM) in present study and significant percent inhibition of PGE_{2} production observed at all dose level compared to LPS control. The results observed by other researchers supported results of present study like Peana et al., (2006) examined the effect of Linalool (0.1 μM, 10 μM and 1000 μM) in lipopolysaccharide (LPS) induced macrophages cell line J774.A1 and found significant reduction of NO and PGE_{2} production in concentration dependent manner; Li et al., (2015) observed significant and dose dependent inhibition of NO and PGE_{2} levels in LPS induced BV2 microglia cells following treatment of Linalool (162, 324, 648 μM) and Kim et al., (2009) evaluated the anti-inflammatory effect of Linalool which is the main content of Illicium anisatum extract (25, 50 and 100 mg/ml) in RAW 264.7 macrophage cells and found dose dependent reduction of nitrite and PGE_{2} production. In present in vivo experiment, significant percent inhibitions of carrageenan induced inflammation were observed following single intramuscular administration of Linalool in comparison with carrageenan control group up to 6 hours. The results of present study are in agreement with percent inhibition observed with Linalool (75 mg/kg) treatment as 38 % and 34 % at 3 and 5 hours after carrageenan administration, respectively (Peana et al., 2002) and percent inhibition of paw edema was observed as 43 ± 9 % and 66 ± 11 % at 4 hours following intraperitoneal administration of Linalool at doses of 50 and 200 mg/kg, respectively in mice (Batista et al., 2010).

In conclusion the linalool possessed in vitro antibacterial activity against various gram positive and gram negative organisms with MIC values ranging from 0.63 to 1.25 mg/ml. Concurrent, in vivo antibacterial efficacy of Linalool was observed in neutropenic rat thigh infection model. Significant decreased NO and PGE_{2} levels in LPS induced RAW 264.7 cells treated with different concentrations of Linalool and significant percent inhibition of carrageenan induced rat paw oedema was noticed following single intramuscular administration of Linalool at dose of 100 mg/kg.

Acknowledgement

I wish to express my gratitude and appreciation to authorities of Veterinary College, Navsari Agricultural University, Navsari, Gujarat for providing me the opportunity and facilities to carryout research work.

Conflict of interest statement

Authors declare that they have no conflict of interest.

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How to cite this article:
Varia, R. D., J. H. Patel, F. D. Modi, P. D. Vihol and Bhavsar, S. K. 2020. In vitro and In vivo Antibacterial and Anti-inflammatory Properties of Linalool. Int.J.Curr.Microbiol.App.Sci. 9(09): 1481-1489. doi: https://doi.org/10.20546/ijcmas.2020.909.187