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Biocompatibility, Antimicrobial and Wound Healing Activities of *Lavandula dentata* Leaves Extract

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ABSTRACT

Background: The human skin is a natural barrier that protects against external stress, but its physiological structure can be compromised when it gets damaged. In the field of medical science, wounds are a significant issue that requires immediate attention. *Lavandula* species are used in the food, perfume and cosmetics industries due to their antimicrobial, anti-inflammatory and wound-healing properties.

Methods: The present study was done to assess the biocompatibility, antimicrobial and wound-healing potential of *L. dentata* leave methanolic extract (LE) that is cultivated in the Taif region of Saudi Arabia. The biocompatibility of LE was analyzed against the normal human skin fibroblast (HSF) cell line using SRB assay. A quarter of LE IC_{50} was used for wound healing assay. Finally, *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Streptococcus pyogenes* were used to determine LE antibacterial potential through the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) measurement.

Result: LE appears safe on HSF cell line with IC_{50} = 97 μg/mL. LE decreased wound width, wound area and the mean cell migratory rate of wound border cells during scratch closure, while increased the wound closure% in a time-dependent manner compared to negative control. LE shows antimicrobial potential against all four strains at MIC and MBC>3.0 mg/mL, except for *Streptococcus pyogenes* MIC= 3.0 mg/mL. In conclusion, LE offers therapeutic benefits against wound healing with an antimicrobial effect, however, higher concentrations of LE should be used to assess its effect.

Key words: Antimicrobial, Cytotoxicity, HSF, Lavender, Wound healing.

INTRODUCTION

The skin is a barrier to protect the body against microorganisms' infection, environmental damage, dehydration, temperature regulation and sensation. Unfortunately, the skin is exposed to various risks that cause abrasion, tearing, or even abrasion, resulting in wounds that disrupt the normal structure and functions of the skin (Lee *et al*., 2006; Ehterami *et al*., 2018). Acute wounds heal normally, while chronic wounds last longer and cause tissue infection, damage and other diseases such as diabetes or venous ulcers (Izzah Ibrahim *et al*., 2018).

Although reactive oxygen species (ROS) are normally produced and act as cellular messengers to stimulate key processes associated with wound healing, including cell motility, cytokine action and angiogenesis (Rodrigues *et al*., 2012). However, impaired wound healing due to nutrition, age, infection, gender and oxygenation increases the formation of ROS and reduces various enzymatic and non-enzymatic free radical scavengers that delay wound healing and cause further tissue damage (Rodrigues *et al*., 2012). Consequently, medicinal herbs, plants and extracts with strong antioxidant and antimicrobial activity are promising healing agents (WHO, 2004).

Lavender (*Lavandula dentata* L.), belonging to the Lamiaceae family, is a widely distributed plant extensively cultivated worldwide. *Lavandula* species extract and oil contain different components including geraniol, linalool, ursolic acid, linalyl acetate and others that are used in various medicinal applications including skin sores treatment, inflammation, pain, gastrointestinal, rheumatic and nervous disorders (Hajhashemi *et al*., 2003). Lavender exhibits strong antioxidant, antibacterial and antiviral activities because many extracts and essential oils derived from lavender have shown potent anti-inflammatory, antibacterial and antioxidant activities (Altaei, 2012; Al Sufyani *et al*., 2019; Schweitzer, 2021). Mori *et al*. (2016) report that lavender oil accelerates granulation and wound contraction through transforming growth factor-β induction *in vivo*. For example, Lavender oil consists mainly of terpenes and terpenoids, with linalool (19-48%), 1, 8 cineole (21-42%) and camphor (5-17%) (Rota *et al*., 2004). Three main *Lavandula* species are principally cultivated to produce essential oils worldwide: *L. angustifolia* (fine lavender), *L. latifolia* (spike lavender) and the sterile hybrid

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L. intermedia (lavandin) due to their extensive and important cosmetic and pharmaceutical applications (Oueslati *et al*., 2020). A systematic review from Saudi Arabia by Ahmad *et al*. (2022) and others in the public domain (Giuliani *et al*., 2020) have reported the medicinal uses and pharmacological properties of Lavender. Here emphasis on the wound-healing potential of *Lavandula dentata* should be done. The current study was undertaken to evaluate the biological (cytotoxic and antimicrobial) and wound-healing activities of *Lavandula dentata* leaf extract that is cultivated in the Taif region of Saudi Arabia.

MATERIALS AND METHODS

The experiment took place at Taif University during the summer of 2023. *L. dentata L.* (fringed/Toothed/French lavender) leaves were freshly collected from Al Shafa area in Taif governorate (a high-altitude region located at an elevation of 1,879 m (6,165 ft) above sea level, with coordinates: 21°16′30.34″N 40°24′22.16″E), Saudi Arabia. They were identified and authenticated by Dr. Hussein, N. R. A. (Botany Department, Faculty of Science, South Valley University, Qena, Egypt) as *Lavandula dentata* L. Sp. Pl.: 572 (1753), Lamiaceae Martinov.

Before use, leaves were rinsed in water, dried away from the sun and ground to obtain fine powder (Fig 1). The powder was mixed with 200 mL of methanol (lab grade). The mixture was macerated overnight and then filtered using filter paper. Later, the marc (the damp solid material after filtration) was macerated again in 200 ml of methanol for 1 h and then filtered, this step was repeated twice. Finally, 600 ml of the collected methanol was evaporated under vacuum at 40°C, yielding 1.289 g of methanolic extract of lavender leaves (LE) (Labarbe *et al*., 1999).

Human Skin Fibroblast (HSF) obtained from Nawah Scientific Inc., (Mokatam, Cairo, Egypt) was used to assess the cytotoxic effect of LE extract. Cells were maintained in Dulbecco's Modified Eagle Medium (DMEM) media supplemented with 100 units/mL of penicillin, 100 mg/mL of streptomycin and 10% of heat-inactivated fetal bovine serum in humidified, 5% (v/v) CO_2 atmosphere at 37°C. HSF cell viability against LE (0.1-1000 μg/mL) was assessed by using sulforhodamine B (SRB) assay according to Allam *et al*. (2018) and Skehan *et al*. (1990). Cisplatin (0.01-100 μg/mL) was used as a positive control. LE cytotoxic effect was calculated as:

Cell viability (%) =

$$\text{Mean OD}_{570nm} \text{ of treated cells/Mean OD}_{570nm} \text{ of control (untreated cells)} \times 100.$$

The data was plotted using OriginLab and the IC_{50} value for LE was determined.

For the wound healing assay, HSF cell lines were cultured in DMEM media, scratched and then treated with fresh media containing ¼ IC_{50} of LE (24.24 μg/mL) at 24, 48, 72 and 96 h. Negative control wells were replenished with fresh medium (only). Images were taken using an inverted microscope at 24, 48, 72 and 96 h intervals. At the end of each timing, the wound width, migration rate, wound area and wound closure % were calculated (as mean±SD) using MII ImageView software version 3.7 according to Main *et al*. (2019) and Martinotti and Ranzato (2019).

The antibacterial effect of lavender leaf extract (serial two-fold dilutions of LE 3 mg/mL to 0.005 mg/mL) was determined by the Clinical and Laboratory Standards Institute (CLSI) methods. Four different bacterial strains were obtained from Nawah Scientific Inc. (Mokatam, Cairo, Egypt) and used in the present study: *Escherichia Coli* ATCC 8739, *Staphylococcus aureus* ATCC 29213, *Pseudomonas aeruginosa* ATCC 9027 and *Streptococcus pyogenes* ATCC 19615. Colony suspension and broth macrodilution were prepared according to EUCAST (2003). An antibiotic, ciprofloxacin (3 mg/mL to 0.005 mg/mL), was used as a positive control. The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of LE against four different aerobic bacterial strains (*Escherichia Coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Streptococcus pyogenes*) were done. The MBC results of LE were analyzed using a one-way ANOVA test. The significance of all the statistical tests was determined at $p<0.05$ using GraphPad Prism 8.0.1 software.

Fig 1: Steps of lavender leaves dryness, collection and grinding to obtain fine powder (A→C).

RESULTS AND DISCUSSION

Lavender leaves extract biocompatibility

Lavandula genus plants have been widely used in traditional medicine due to their high content of bioactive compounds (Oueslati *et al*., 2020). Those bioactive compounds include monoterpenes, polyphenols and sesquiterpenes (Areias *et al*., 2000). Those constituents give lavender various properties such as antiseptic, anti-inflammatory, analgesic, antioxidant, antimicrobial and antifungal activities (Chrysargyris *et al*., 2016; El Abdali *et al*., 2022). Therefore, extracts of lavender have been used in the food, perfume and cosmetics industries (Wells *et al*., 2018). In the present study, we aimed to evaluate the biological properties of *L. dentata* L. leaves extract (LE) that are collected in Saudi Arabia, Taif region.

In the cell viability assay on human skin fibroblast (HSF), Fig 2A shows a high cytotoxic effect of Cisplatin (positive control, 0.001-100 μg/mL) in a dose-dependent manner with IC_{50}= 0.78 μg/mL, while LE appears to be safer on the same cell line. LE at concentrations of 0.01, 0.1, 1, 100 and 1000 μg/ml decreased cell viability dose-dependently with IC_{50}= 97 μg/mL (Fig 2B). Our data indicate that LE has low cytotoxicity *in vitro* at low concentrations, which agrees with Cardia *et al*. (2018). They have reported mice leukocytes viability >75% up to a concentration of 10 μg/mL of *L. angustifolia* oil (LAO) using MTT Assay. However, LAO at higher concentrations (30 and 90 μg/ml) affected cell viability. They concluded that LEO has a cytotoxicity dose-dependent manner and can vary with its constituents (Prashar *et al*., 2004). In addition, Alnamer *et al*. (2012) have reported the non-toxic potential of *L. officinalis* extract as an oral administration. *L. dentata's* low cytotoxicity could be attributed to its antioxidant potential. Moroccan *L. dentata* oil consists of 16 constituents with the major component being linalool (45.06%), then camphor (15.62%) and borneol (8.28%) making it an effective natural agent against free radical damage (El Abdali *et al*., 2022).

Wound healing assay

The skin represents the largest organ in the body that acts as a biological barrier against injuries, burns, illness and any external stress (Mssillou *et al*., 2022). A wound is a tissue injury because of several chronic diseases including diabetes, trauma and cancer, which are among the major clinical problems (Shrivastav *et al*., 2018; Valente *et al*., 2019). Worldwide, 6 million people are suffering from non-healing wounds (85% of aged persons) resulting in enormous healthcare expenditures (Paladini and Pollini, 2019). The recovery period of a wound might take a few days in healthy people, which is prolonged in acute, while impaired in chronic wounds (Yadav *et al*., 2021). The wound healing process includes four phases: hemostasis, inflammation, proliferation and remodeling (Belachew *et al*., 2020). Several medicinal plants have been proven to increase

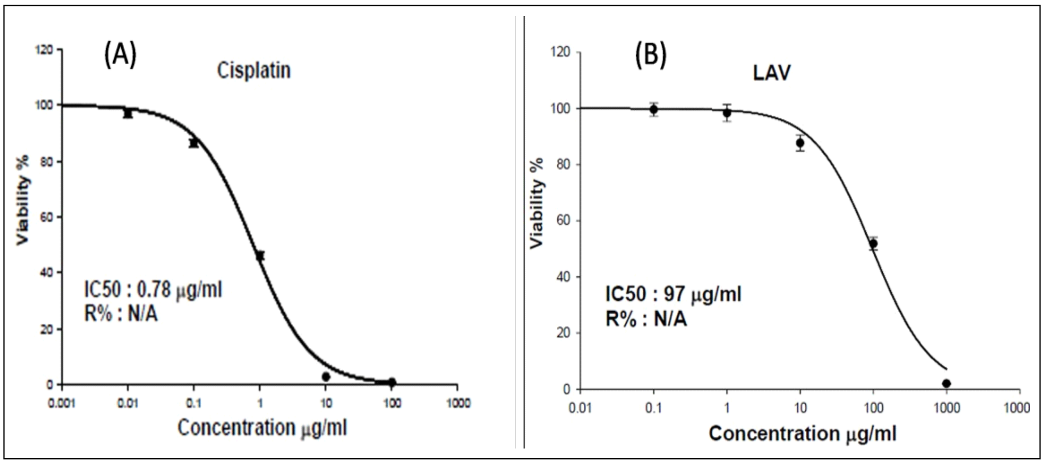


Fig 2: Cell viability % of HSF for Cisplatin (A) and LE (B) treatment after 72 h.

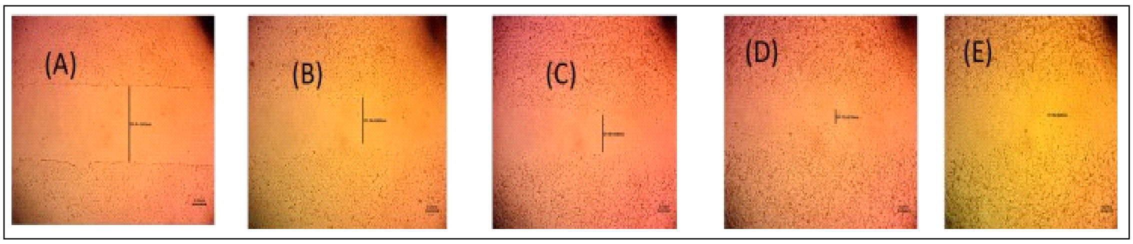
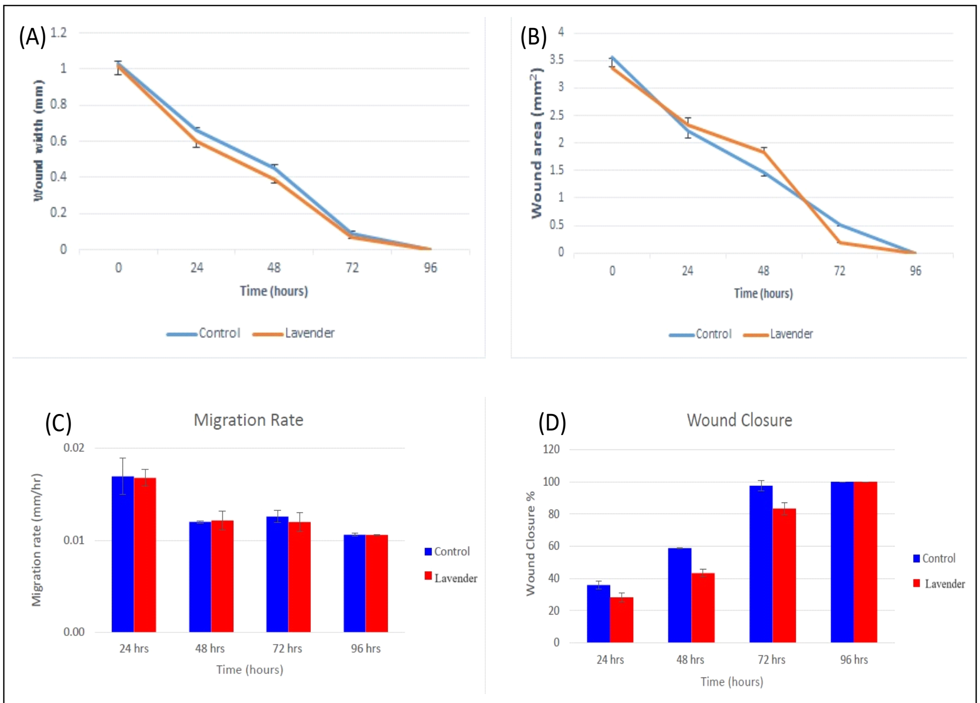


Fig 3: Representative images from *in vitro* scratch wound healing assays for HSF cells treated by LE at 0 (A), 24h (B), 48h (C), 72h (D) and 96 (E) interval time.

the renewal rate of damaged tissues *in vivo*, *in vitro* and in excisional and incisional experimental models such as *Nepeta dschuparensis*, *Chamaecostus cuspidatus*, *Nigella sativa*, *Aristolochia saccate* and others (Bolla *et al*., 2019; Low *et al*., 2021; Naeimi *et al*., 2020; Ponnanikajamideen *et al*., 2019; Sallehuddin *et al*., 2020).



Bar graph illustrating the mean cell migratory rate of wound border cells during scratch closure (C) and wound closure % at indicated time points (D) during the scratch wound assay.

Fig 4: Graph showing wound width (A) and wound area (B) in the presence of LE (24.24 µg/mL) at different interval times (0, 24 h, 48 h, 72 h and 96 h) in comparison to control.

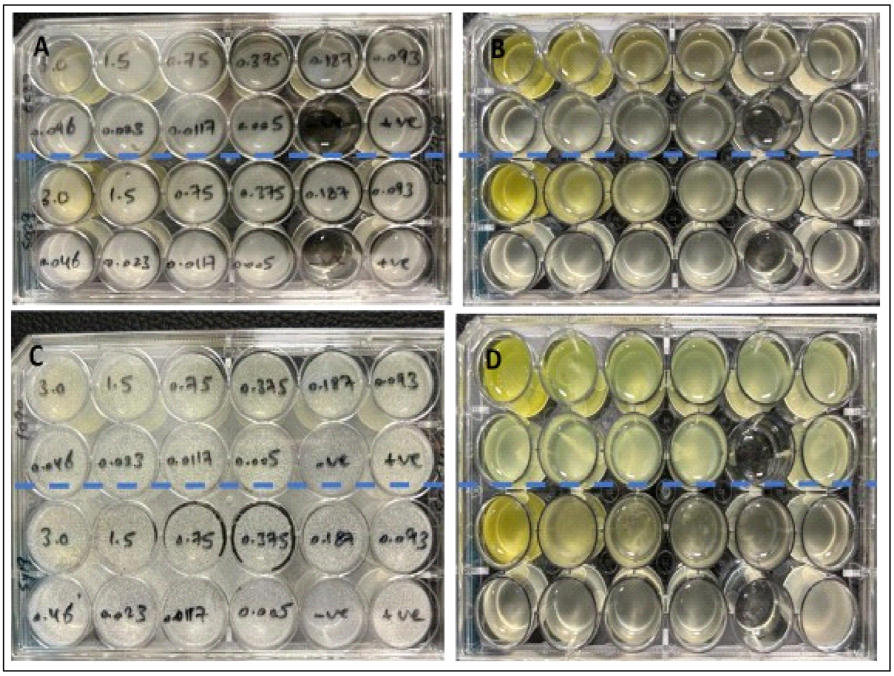


Fig 5: Lavender leaf extract potential against *E. coli* (upper half of plates A,B), *S. aureus* (lower half of plates A,B), *P. aeruginosa* (upper half of plates C,D) and *S. pyogenes* (lower half of plates C,D).

We have chosen one of the commonly used medicinal plants that are cultivated in KSA and used in numerous therapies, *Lavandula dentata.* Saudi Arabia has a diverse flora comprising different species that include numerous medicinal plants due to its vast area of diverse geographical landscapes and climates. Therefore, ethnomedical native plants are traditionally used in KSA for therapy, including wound healing Aati *et al* (2019). According to Fig 3 (A-E), several parameters are measured to determine the wound-healing potential of LE methanolic extract (a quarter of IC_{50}=24.24 µg/mL) at 0, 24 h, 48 h, 72 h and 96 interval time. We have chosen ¼ of IC_{50} as a safe dose for LE treatment to prevent cell death (HSF cells) at higher doses. We have determined that LE decreased wound width (Fig 4A) and wound area (Fig 4B) in a time-dependent manner (0, 24 h, 48 h, 72 h and 96 h) in comparison to negative control. In addition, LE (24.24 µg/mL) decreased the mean cell migratory rate of wound border cells during scratch closure (Fig 4C) and increased the wound closure % (Fig 4D). However, for all parameters of the wound healing assay, there is a non-significant difference between LE treatment and the negative control group at different interval times. This could be returned to the selected very low dose of LE treatment for skin fibroblast cells. From a long time ago until now, different plants have been used in wound healing as a traditional medicine in KSA regions such as leaves and whole plant *of Blepharons ciliaris* L., leaves of *Ecbolium gymnostachyum*, leaves of *Hypoestes forsskalii*, whole plant of *Euryops arabicus Steud* (Al-Sodany *et al*., 2013), *Adenium arabicum Balf*, leaves of *Centaurothamnus* maximus, leaves of *Verbesina* encelioides, leaves and seeds of *Diplotaxis acris (Forssk) Boiss* (El-Shabasy, 2016), fruits of *Tamarindus indica* L. (Aly *et al*., 2022) and others (Aati *et al*., 2019).

Leaves and flowers of *Lavandula dentata* L. have been used for headache, relieve rheumatic pain and cold (Al-Sodany *et al*., 2013) but in our peer knowledge, it is the first time to assess the wound healing potential of *Lavandula dentata* cultivated in KSA. It was reported that L. *dentata* extracts consist of many compounds, but the major constituents are linalool, camphor and borneol which belong to oxygenated monoterpenes, β-farnesene which belongs to Sesquiterpene hydrocarbons and 1,8 cineole. It was reported that the concentration of LE constituents differs from one cultivated region to another such as in eastern Morocco (Imelouane *et al*., 2009), Moroccan middle Atlas (Soro *et al*., 2014), Brazil (Justus *et al*., 2018) and Italy (Giuliani *et al*., 2020). The chemical composition of LE varied depending on the mplant part (roots, leaves and flowers) from which it was extracted, geographical origins, seasonal changes, harvest time, genetic variability and growth conditions (Bouyahya *et al*., 2023). Natural compounds present in medicinal plants can accelerate the wound healing process by promoting epithelization (Farzaei *et al*., 2015), increasing vasculogenesis and angiogenesis (Caban and Lewandowska, 2021) and modulating the inflammatory cytokines (Hu *et al*., 2011) and finally enhancing wound contraction rates (Yin *et al*., 2015).

Table 1: Minimum inhibitory concentration (MIC) and minimum bactericidal concentrations (MBC) of lavender leaf extract (LE).

Bacterial strai	LE concentration mg/mL	
	MIC	MBC
Escherichia coli 8739	> 3.0	> 3.0
Pseudomonas aeruginosa 9027	> 3.0	> 3.0
Staphylococcus aureus 29213	> 3.0	> 3.0
Streptococcus pyogenes 19615	3.0	> 3.0

Antimicrobial potential of LE

Four different bacterial strains were selected because they are common in wound infections: *E. coli*, *S. aureus*, *P. aeruginosa* and *S. pyogenes* (Puca *et al*., 2021). Antimicrobial resistance is considered a top ten threat to global health according to the World Health Organization (WHO, 2019). This resistance returns to the inappropriate use of antimicrobial drugs in humans and the unpleasant appearance of multi-drug resistant strains, which represents a public health concern. The WHO report indicates high annual deaths due to multi-drug resistant pathogens in Europe (25,000 deaths/year) and the United States (23,000 deaths/year). In addition, about 50% of infections are associated with *K. pneumoniae*, *E. coli*, *S. aureus* and *P. aeruginosa* (Pallavali *et al*., 2017; WHO, 2014). Therefore, the present study has been established for the antimicrobial assessment of the methanolic extract of LE.

Fig 5 and Table 1 show the antibacterial potential of LE against aerobic bacterial strains that infect wounds: Gram-negative (*E. coli* and *P. aeruginosa*) and Gram-positive (*S. aureus* and *S. pyogenes*). Table 1 shows that LE has a higher antimicrobial effect against all four strains at MIC and MBC> 3.0 mg/mL, except for *Streptococcus pyogenes* MIC= 3.0 mg/mL. However, ciprofloxacin has a higher antimicrobial effect at MIC<0.005 mg/mL. In agreement with our results, El-Said *et al*. (2021) in Saudi Arabia tested essential oil extracted from flowering aerial parts of L. *pubescens* against 13 strains of Gram-negative and Gram-positive bacteria using the agar diffusion assay. Their results revealed that LE had antimicrobial potential, but Gram-negative strains were more susceptible than Gram-positive ones. In addition, Hossain *et al*. (2017) tested the flowering part of *L. angustifolia* in Bulgaria against various pathogenic bacteria isolated from pet turtles belonging to seven species: *Aeromonas hydrophila*, *Aeromonas caviae*, *Citrobacter freundii*, *Proteus mirabilis*, *Salmonella enterica, Aeromonas dhakensis* and *Ps. aeruginosa*. Their results reported the LE antibacterial effect against all tested strains except *Ps. aeruginosa*.

The major chemical constituents of the LE (linalool, linalyl acetate and terpinen-4-ol) are responsible for the antimicrobial effect. These components damage the lipid layer of the cell membrane, which results in bacterial cell leakage and death (De Rapper *et al*., 2016). Recently, it has been reported that lavender essential oil induces oxidative stress on bacterial cells, disrupts their membrane and then dies through proteomic and genomic analyses (Yang *et al*., 2020, Yang *et al*., 2021). Further study is needed to report the specific mode of action of LE against bacterial strains.

CONCLUSION

The methanolic extract of *L. dentata* is safe for skin treatment, with low cytotoxic effects on skin fibroblast cells. It has potential in wound healing and as an antimicrobial agent, but further studies are needed to determine the optimal concentrations and the exact mechanism of action. Additional research is required to assess how the extract's major constituents vary across different geographical regions.

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Author contributions

The authors contributed to the practical part, writing the original draft, editing and accepting the final version of this article.

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Conflict of interest

The authors declare no conflict of interest.

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