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Antibacterial and anti-inflammatory properties of *Santalum spicatum* (R.Br.) A.DC. and *Santalum album* L. essential oils: activity against clinical isolates, modulation of ROS production in keratinocytes, and inhibition of eicosanoid pathway enzymes

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ABSTRACT

Ethnopharmacological relevance: Products derived from *Santalum* species have been valued for centuries in religious practices and traditional Chinese and Indian medicine for treating various conditions, including inflammatory and skin disorders.
Aim of the study: This study investigated the impact of two essential oils, *S. album* L. and *S. spicatum* (R.Br.) A.DC. on bacterial isolates obtained from skin samples, as well as their impact on mammalian cells and enzymes involved in the eicosanoid cascade.
Materials and methods: Chemical composition was analyzed by GC–MS. Antibacterial activity against clinical isolates was assessed by broth microdilution to determine minimum inhibitory (MIC) and minimum bactericidal concentrations (MBC). Cytotoxicity in HaCaT and HFF-1 cells was evaluated using the MTT and ROS assays. Inhibition of 5-lipoxygenase (5-LOX), cyclooxygenase (COX), and phospholipase A_2 (PLA_2) was also determined.
Results: α-Santalol and β-santalol were identified in both essential oils, with higher relative abundance in *S. album*. Both oils were active against Gram-positive isolates, with MIC values of 15.625–62.5 μg mL^{-1} and MBC values of 31.25–125 μg mL^{-1}, showing bactericidal activity. No evident cytotoxicity and inhibition of ROS was observed below 500 μg mL^{-1}. Both oils inhibited 5-LOX (*S. album*, 82.29 ± 8.85 μg mL^{-1}; *S. spicatum*, 121.33 ± 52.03 μg mL^{-1}) and PLA_2 (100.12 ± 41.36 and 114.21 ± 17.25 μg mL^{-1}, respectively), while *S. spicatum* also showed COX inhibitory activity.
Conclusions: These findings demonstrate *in vitro* antibacterial activity against Gram-positive clinical isolates and modulation of eicosanoid-related enzymes, supporting further investigation of the biological relevance of both essential oils in inflammatory processes.

1. Introduction

Species belonging to the genus *Santalum*, commonly referred to as sandalwood, are obligate hemiparasite trees or shrubs belonging to the Santalaceae family (Subasinghe, 2013). Native to regions including India, Sri Lanka, the Hawaiian Archipelago, eastern Indonesia, and Australia, these species are widely valued worldwide for their essential oil (Rajarajan et al., 2025).

Traditionally, essential oils and other products derived from *Santalum* spp. have been used for religious and medicinal purposes. They are frequently referenced in mythology, folklore, and religious traditions and have played an important role in spiritual and ceremonial practices across diverse cultures. In ancient Egypt it was used in embalming and offerings, while in Hinduism it played a role in sacred ceremonies

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(Arunkumar et al., 2012; Sharifi-Rad et al., 2023). Its use in multiple religions highlights its broad cultural importance. In addition, sandalwood and its derivatives have long been recognized for their medicinal value. Sandalwood has been widely used in traditional medical systems, particularly in Chinese and Indian medicine, for the treatment of a broad range of conditions (Moy and Levenson, 2017). Traditionally, species of the *Santalum* genus have been used as anti-inflammatory, immunostimulant, antipyretic, and antidiarrheal agents, as well as for the treatment of colds and coughs (Sharifi-Rad et al., 2023). It is also used as an ingredient in complex traditional formulations for the management of a wide range of conditions, including skin disorders (Biswas et al., 2016; Guo et al., 2014).

Among the different species of sandalwood, Indian sandalwood (*S. album* L.), known as the "Royal Tree" in India, is particularly valued for its highly fragrant wood and high essential oil content. Other notable species used for sandalwood oil production include Australian sandalwood (*S. spicatum* (R.Br.) A.DC.) and Hawaiian sandalwood (*S. ellipticum* Gaudich.) (Santha and Dwivedi, 2015; Sharifi-Rad et al., 2023). The essential oil obtained from this species is broadly used in aromatherapy, fragrance and cosmetic sectors. In addition, several works have highlighted its biological activities (Guo et al., 2014; Rajarajan et al., 2025).

Skin and soft tissue infections are caused by the invasion of pathogenic microorganisms into the skin and underlying tissues, resulting in a wide range of clinical presentations, from superficial and uncomplicated infections to severe forms associated with significant morbidity. Their incidence and healthcare burden are increasing, particularly in specific patient populations, such as those with diabetes mellitus, who exhibit greater susceptibility due to impaired wound healing and immune dysfunction (Dryden et al., 2015; Grossi et al., 2022; Kaye et al., 2019; Prodinger et al., 2025). In particular, the infections caused by *Staphylococcus aureus* (*S. aureus*) represent a significant concern in many countries. In fact, *S. aureus* strains resistant to methicillin (MRSA) have been identified by the WHO as a high-priority bacterial pathogen because of its clinical impact and the increasing challenges associated with its treatment (Suaya et al., 2014; World Health Organization, 2024). Given the clinical relevance of microbial infections and the growing need for alternative antimicrobial strategies, increasing attention has been devoted to the antimicrobial properties of medicinal plants and their major bioactive compounds against both bacterial and fungal pathogens (Feng et al., 2025; Gao et al., 2025; Wang et al., 2024; Zhang et al., 2026).

In addition to acute infections, impaired progression through the normal, orderly, and timely sequence of repair can lead to the development of chronic wounds. The management of these chronic wounds remains a major clinical challenge and persistent inflammation in the wound environment is difficult to control (Raziyeva et al., 2021). In chronic wounds, sustained inflammatory responses prevent effective resolution of infection and are recognized as a key factor underlying delayed tissue repair and disease persistence. While inflammation is an essential component of the host defence response, excessive or dysregulated inflammation can be detrimental. In many infectious conditions, tissue injury and disease severity are driven not only by the pathogen itself but also by an exaggerated immune response, characterized by excessive cytokine production and prolonged activation of inflammatory pathways. This hyperinflammatory state can result in collateral tissue damage, impaired repair, and loss of tissue function, ultimately outweighing the protective benefits of pathogen clearance (Chen et al., 2017; Fajgenbaum and June, 2020). In this context, natural products and their compounds have been studied for their anti-inflammatory properties in previous works (Hou et al., 2024; Shi et al., 2022; Tan et al., 2025; Wang et al., 2025).

Given the rising incidence and burden of skin infections and inflammation, along with the traditional use of sandalwood for skin ailments, this study evaluated the effects of two sandalwood essential oils on clinical bacterial isolates. The novelty of this study lies in the integrated and comparative evaluation of both the antibacterial and anti-inflammatory properties of *Santalum album* and *Santalum spicatum* essential oils, together with their chemical composition. Assessing these two biological activities within the same experimental framework provides a more comprehensive understanding of their bioactive potential. Chemical profiling of the essential oils was performed to compare the composition of both oils and identify differences in the relative abundance of their main constituents. Their impact on human cell lines derived from keratinocytes (HaCaT) and fibroblasts (HFF-1) was also assessed. In addition, anti-inflammatory-related properties of the essential oils were investigated by examining their inhibitory activity on enzymes involved in the eicosanoid cascade.

2. Material and methods

2.1. Essential oils

The essential oils from *S. spicatum* (R.Br.) A.DC. (batch 1002) and *S. album* L. (batch 2002) were purchased from Santanol® (Pure Sandalwood) (Santanol Pty Ltd, Canning Vale, Perth, WA, Australia). Both essential oils were of gold-with a declared purity of 100% (1 g/g).

2.2. GC-MS analysis of the essential oils

The two sandalwood essential oils (*S. spicatum* and *S. album*) were studied employing a Agilent 8890 GC system equipped with a single quadrupole 5977 B mass spectrometer and an auto-sampler PAL RTC120. The essential oils were diluted in *n*-hexane (1:100 ratio) and injected in split mode 1:200. The analytes were separated by using an HP-5MS (5% phenylmethylpolysiloxane, 30 m × 0.25 mm, 0.25 μm, Agilent) capillary column as stationary phase. Analytical conditions and the compounds identification were previously reported by Rosato et al. (2021) (Rosato et al., 2021). The density of the two essential oils was determined by using an oscillating U-tube densimeter operating at 20 °C (DA-100M, Mettler Toledo, Greifensee, Switzerland) and was of 0.978 and 0.963 g/mL, for *S. album* and *S. spicatum*, respectively. The refractive index was measured using an Abbe refractometer (NAR-1T LIQUID, Atago Co., LTD, Minato-ku, Tokyo, Japan) at 20 °C and was of 1.5025 and 1.5015, for *S. album* and *S. spicatum*, respectively.

2.3. Bacterial assays

Clinical bacterial isolates of human origin were recovered from different types of infections and lesions, including diabetic foot infections, ulcers, wound specimens (both surgical and non-surgical), otic samples, and exudates. Bacterial isolates were analyzed in the Microbiology Laboratory of Hospital Clínico Universitario Lozano Blesa and identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) using the MALDI Biotyper Sirius platform (Bruker Daltonics, Bremen, Germany). Antimicrobial susceptibility was assessed according to routine laboratory procedures. Each bacterial strain included in the study corresponded to a single clinical isolate obtained from the hospital microbiology laboratory. The corresponding antimicrobial resistance patterns are summarized in the Supplementary Material (Supplementary material 1).

2.3.1. Minimum inhibitory concentration

The minimum inhibitory concentrations (MICs) of the essential oils were evaluated by broth microdilution assays using sterile 96-well microplates as described in previous works (Reigada et al., 2025). Prior to testing, bacterial cultures were standardized to a turbidity equivalent to 0.5 McFarland. The inocula were subsequently diluted to obtain a final concentration of 1×10^{6} CFU/mL in each well, using either Tryptic Soy Broth (Thermo Fisher Scientific) or Mueller–Hinton Broth supplemented with 3% lysed horse blood (Beckman Coulter Inc.), depending on the growth requirements of the bacterial species. Essential oil samples were prepared in the corresponding culture medium with

dimethyl sulfoxide (DMSO; Thermo Fisher Scientific) as a co-solvent, ensuring a final DMSO concentration $\leq$ 0.5%. Appropriate negative and solvent controls were included in all assays. Following incubation at 37 °C for 18–24 h, the MIC was recorded as the lowest concentration of the tested compound that completely inhibited visible bacterial growth, evidenced by the absence of turbidity. Additional control wells were used to verify the initial inoculum density. All experiments were conducted independently on three occasions, with a minimum of three technical replicates per experiment.

2.3.2. Minimum bactericidal concentration

After MIC determination, MBC values were obtained by subculturing aliquots from growth-inhibited wells onto Mueller–Hinton agar or Chocolate agar (BioMérieux), depending on the bacterial strain. Following incubation, colony counts were used to identify the lowest concentration causing a 99.9% reduction in bacterial viability. All assays were performed in triplicate. The antibacterial mode of action was assessed using the MBC/MIC ratio, with values $\leq$ 4 indicating bactericidal activity and values $>$ 4 indicating bacteriostatic activity.

2.4. Cell assays

2.4.1. Cytotoxicity assessment

HaCaT cells and HFF-1 cells were used as *in vitro* models to investigate the cytotoxic effects of the essential oils. The HaCaT and HFF-1 cell lines were obtained from CliniSciences (CLS) and the American Type Culture Collection (ATCC), respectively. Cells were cultured in Dulbecco's Modified Eagle Medium (DMEM; Gibco) supplemented with 1 mM sodium pyruvate, 1% penicillin–streptomycin, and fetal bovine serum (Thermo Fisher Scientific) at 10% and 15% for HaCaT and HFF-1 cells, respectively, in accordance with the manufacturers' guidelines. Cell cultures were incubated at 37 °C in a humidified atmosphere with 5% CO_2.

Cytotoxicity was determined using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay, according to a previously described procedure (Millán-Laleona et al., 2025). Briefly, cells were seeded at a density of 2×10^4 cells and incubated for 24 h to allow attachment. The medium was then replaced with fresh DMEM supplemented with varying concentrations (31.25–2000 μg mL^{-1}) of either *S. album* or *S. spicatum* essential oil, whereas untreated control cells received DMEM alone. After a 24 h treatment period, MTT solution was added (0.4 mg mL^{-1}), followed by a 2 h incubation in the absence of light. Formazan formation was quantified by solubilizing the crystals in DMSO and measuring absorbance at 550 nm. Experiments were repeated independently a minimum of three times. CC_{50} values were estimated from the dose–response relationships obtained.

2.4.2. Inhibition of ROS production

HaCaT cells were pretreated overnight with different concentrations of the essential oils. Following incubation, intracellular reactive oxygen species (ROS) production was evaluated using 2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA) (Sigma-Aldrich) as a fluorescent probe. Oxidative stress was induced by exposing the cells to 500 μM H_2O_2 to promote intracellular ROS generation. Fluorescence intensity, as an indicator of ROS production, was monitored at an excitation wavelength of 480 nm and an emission wavelength of 510 nm at 37 °C for 90 min.

2.5. Enzymes

2.5.1. 5-Lipoxygenase inhibition

The effect of the essential oils on 5-lipoxygenase (5-LOX) was determined according to Cebollada et al. (2024) (Cebollada et al., 2024).

Assays were conducted in UV-transparent flat-bottom 96-well microplates (Corning®). Briefly, each well contained buffer, the diluted essential oil sample, soybean-derived 5-LOX (VidraFoc). Following pre-incubation at room temperature for 5 min, the reaction was started by adding of linoleic acid (VidraFoc). The formation of the reaction product was monitored at 234 nm. Each assay was performed in triplicate across a minimum of three independent experiments.

2.5.2. Phospholipase A_2 inhibition

Phospholipase A_2 (PLA_2) inhibitory activity was determined using the $sPLA_2$ (Type V) Inhibitor Screening Assay Kit PC substrate (Item No. 10004883 Cayman Chemical). Essential oils were tested at concentrations between 31.25 and 500 μg mL^{-1}, and absorbance was measured at 405–420 nm. A known PLA_2 inhibitor provided in the commercial kit was used as a positive control. Assays were conducted in triplicate.

2.5.3. Cyclooxygenase inhibition

Cyclooxygenase (COX) inhibition was determined using a colorimetric COX Inhibitor Screening Assay Kit (Cayman Chemical; Item No. 701050) according to the manufacturer's instructions. Essential oils dissolved in ethanol were evaluated at concentrations from 15.63 to 62.50 μg mL^{-1}. Enzyme activity was quantified spectrophotometrically at 590 nm following substrate addition. All experiments were performed in triplicate.

2.5.4. Tyrosinase inhibition

Tyrosinase inhibitory activity was evaluated as an additional method to further investigate the dermatological potential of the essential oils, particularly their possible application in the modulation of skin pigmentation. The assay was performed in 96-well microplates. Each reaction mixture contained 80 μL of potassium phosphate buffer (pH 6.8), 40 μL of L-DOPA solution (Thermo Fisher Scientific), and 40 μL of tyrosinase solution (Sigma-Aldrich), with both L-DOPA and the enzyme prepared in the same buffer. Enzyme inhibition was assessed spectrophotometrically by measuring the absorbance at 475 nm. For each sample, three independent experiments were conducted, with all measurements performed in triplicate. Kojic acid was included as a positive control.

2.6. Toxicity assessment using brine shrimp lethality test

Adult *Artemia salina* (*A. salina)* were used as an alternative model organism to evaluate toxicity. Groups of ten adults were exposed to essential oils ranging from 500 to 31.25 μg mL^{-1} in seawater. A control group consisting of organisms maintained in seawater without treatment was included in the experiment. After 24 h, the number of dead individuals in each condition was recorded. Mortality percentages were calculated and corrected for natural mortality observed in the untreated control using Abbott's formula. All experiments were performed in triplicate. 50% lethal dose (LD_{50}) was determined.

2.7. Statistical analysis

GraphPad Prism 10 was used to analyse results. Outliers were detected using Grubbs' test and excluded when statistically significant. Statistical differences between treated samples and untreated controls were assessed using one-way analysis of variance (ANOVA), followed by Dunnett's multiple-comparison post hoc test. CC_{50} and IC_{50} values were obtained from non-linear regression analyses of the cytotoxicity and enzymatic inhibition dose–response curves, respectively. The MBC/MIC ratio was used to determine whether the antibacterial activity was bactericidal or bacteriostatic. In addition, the selectivity index (SI) was calculated as the ratio between CC_{50} and MIC values to estimate the selectivity of the compounds toward bacterial targets relative to mammalian cells.

Table 1
Chemical profile of the essential oils obtained from *S. spicatum* and *S. album*.

No	Compound[a]	RI[b]	RI Lit.[c]	*S. spicatum* Area %[d]	*S. album* Area %[d]	Id[e]
1	Furfurylpyrrole	1183	1185	-	tr[f]	RI, MS
2	*α*-Cedrene	1413	1410	0.1	-	RI, MS
3	*α*-Santalene	1421	1424	0.6	0.5	RI, MS
4	*α*-(*E*)-Bergamotene	1436	1432	0.1	tr	RI, MS
5	*epi-β*Santalene	1448	1445	0.3	0.6	RI, MS
6	*β*-Santalene	1461	1457	0.6	1.1	RI, MS
7	*α*-Acoradiene	1465	1464	0.1	-	RI, MS
8	*ar*-Curcumene	1483	1479	0.6	0.1	RI, MS
9	*β*-Curcumene	1512	1514	0.7	tr	RI, MS
10	Sesquicineole	1514	1515	0.2	-	RI, MS
11	(*E*)-Nerolidol	1564	1561	1.5	-	RI, MS
12	Dendrolasin	1574	1570	1.9	-	RI, MS
13	Guaiol	1599	1600	0.1	-	RI, MS
14	(*Z*)-*α*-Santalol	1677	1674	20.4	48.6	RI, MS
15	*α*-Bisabolol	1686	1685	8.4	-	RI, MS
16	(*Z*)-*α*-*trans*-Bergamotol	1692	1690	4.3	5.9	RI, MS
17	(*Z*)-*epi*- *β*-Santalol	1704	1702	1.6	5.0	RI, MS
18	(*Z*)-*β*-Santalol	1718	1715	7.2	22.3	RI, MS
19	(*2Z,6E*)-Farnesol	1721	1722	7.6	-	RI, MS
20	(*Z*)-Nuciferol	1726	1724	18.4	2.3	RI, MS
21	(*E*)-*β*-Santalol	1740	1738	0.5	1.1	RI, MS
22	*β*-(*Z*)-Curcumen-12-ol	1757	1754	8.0	1.0	RI, MS
23	(*Z*)-Lanceol	1762	1760	3.4	2.7	RI, MS
	Total identified (%)			86.6	91.3	
	Chemical classes					
	Sesquiterpene hydrocarbons (%)			3.2	2.4	
	Oxygenated sesquiterpenes (%)			83.4	88.8	
	Others (%)				tr	

[a] Compounds are listed according to their order of elution on the HP-5MS capillary column.
[b] Linear retention index calculated according to the Van den Dool and Kratz formula (van Den Dool and Dec. Kratz, 1963).
[c] Retention index taken from Adams.
[d] Relative percentage values are mean of two independent analyses.
[e] Identification methods: RI, coherence of the calculated RI with those stored in the ADAMS (2007) and NIST 17 (2017) libraries (Adams, 2007; National Institute of Standards and Technology, 2017); MS, mass spectrum matching with respect to ADAMS, FFNSC (2012) and NIST 17 MS libraries (FFNSC, 2012).
[f] Tr, traces if area < 0.1%.

3. Results

3.1. Chemical composition

The composition of essential oils was determined by GC-MS (see Table 1). For *S. spicatum*, the total of identified compounds was 86.6% whereas for *S. album* 91.3%. Both essential oils were characterized by the predominance of oxygenated sesquiterpenes. Indeed, *S. album* chemical composition was mainly characterized by (*Z*)-*α*-santalol (48.6%) and (*Z*)-*β*-santalol (22.3%), while minor compounds were (*Z*)-*α trans*-bergamotol (5.9%), (*Z*)-epi-*β*-santalol (5.0%), (*Z*)-lanceol (2.7%), and (*Z*)-nuciferol (2.3%). As regards to *S. spicatum* essential oil, its chemical composition was dominated by (*Z*)-*α*-santalol (20.4%) and (*Z*)-nuciferol (18.4%), while minor constituents were *β*-(*Z*)-curcumen-12-ol (8.0%), (*Z*)-*β*-santalol (7.2%), (*Z*)-*α*-*trans*-bergamotol (4.3%), (*Z*)-lanceol (3.4%), dendrolasin (1.9%), (*Z*)-epi-*β*-santalol (1.6%), and (*E*)-nerolidol (1.5%).

3.2. Antibacterial activity

Table 2 presents the antibacterial activity of both essential oils against the clinical isolates evaluated in this study. Essential oils from *S. album* and *S. spicatum* exhibited identical MIC values for several isolates, including *Streptococcus agalactiae* (*S. agalactiae*) (31.25 μg mL^{-1}), oxacillin-susceptible *S. aureus* isolated from non-surgical wound (31.25 μg mL^{-1}), and other *S. aureus* isolates (62.5 μg mL^{-1}). In contrast, for *Streptococcus anginosus* (*S. anginosus*) and *Staphylococcus lugdunensis (S. lugdunensis), S. album* essential oil showed lower MIC values compared to *S. spicatum*. Additionally, *S. album* also presented lower MBC values for *S. agalactiae,* and *S. aureus* isolated from exudate samples. MIC and MBC values for Gram-negative isolates exceeded 1000 μg mL^{-1}.

Table 2
MIC and MBC values (μg mL^{-1}) of *S. spicatum* and *S. album* essential oils against clinical isolates. MIC and MBC values are reported as the modal values obtained from at least three independent experiments. Each row represents an individual clinical isolate.

		S. spicatum MIC μg mL^{-1}	*S. album* MIC μg mL^{-1}	*S. spicatum* MBC μg mL^{-1}	*S. album* MBC μg mL^{-1}
Streptococcus agalactiae	Diabetic foot	31.25	31.25	62.5	31.25
Streptococcus anginosus	Surgical wound	31.25	15.625	31.25	31.25
Staphylococcus lugdunensis	Otic	62.5	31.25	125	125
Staphylococcus aureus [a]	Non-surgical wound	31.25	31.25	125	125
Staphylococcus aureus	Exudate	62.5	62.5	125	62.5
Staphylococcus aureus [b]	Non-surgical wound	62.5	62.5	125	125
Staphylococcus aureus	Ulcer	62.5	62.5	125	125
Morganella morgani	Non-surgical wound	>1000	>1000	>1000	>1000
Escherichia coli	Non-surgical wound	>1000	>1000	>1000	>1000
Pseudomona aeruginosa	Non-surgical wound	>1000	>1000	>1000	>1000
Pseudomona aeruginosa	Ulcer	>1000	>1000	>1000	>1000

[a] Oxacilin susceptible.
[b] Oxacilin resistant.

3.3. Cell assays

3.3.1. Cytotoxicity

HaCaT and HFF-1 cells were treated with essential oils at a range of concentrations from 2000 to 31.25 μg mL^{-1} for 24h, cell viability being measured with the MTT assay. Neither essential oil exhibited evident cytotoxic effects at concentrations below 500 μg mL^{-1}, with cell viability remaining close to 100% (see Fig. 1). Concentrations of 1000 and 2000 μg mL^{-1} were additionally evaluated to determine the CC_{50} values. The calculated CC_{50} for the HaCaT cell lines values were 891.30 ± 18.23 μg mL^{-1} and 935.22 ± 35.51 μg mL^{-1} for *S. album* and *S. spicatum* respectively. For the HFF-1 cell line the CC_{50} values were 1308.56 ± 304.23 μg mL^{-1} (*S. album*) and 1217.36 ± 38.28 μg mL^{-1} (*S. spicatum)*.

3.3.2. ROS production

The impact of both essential oils on ROS production in HaCaT cells stressed with H2O2 is presented in Fig. 2. Fig. 2A shows the evolution of the % of ROS normalized with the initial untreated control over time, while Fig. 2B shows these results as the normalized AUC to better compare results. At concentrations 125 and 62.5 both essential oils reduced the ROS production, showing levels close to those exhibited by the negative control. The stressed control, not treated with essential oil showed increasing ROS production reaching values of 296.82%. At 31.25, both essential oils did not showed ROS inhibition showing similar values to the stressed control.

3.4. Selectivity index and MBC/MIC ratio

As shown in Table 3, both essential oils herein tested were found to be bactericidal for all the Gram-positive bacteria tested in this work, displaying ratios lower or equal to 4. On the other hand, a selectivity index (SI) was determined comparing the MIC values and the CC_{50} values obtained for both HaCaT and HFF-1 cells. In all cases, the SI was higher than 10, showing good selectivity towards the bacteria while displaying low cytotoxic profile for the human cell lines.

3.5. Enzymatic assays

In Fig. 3 the impact of both essential oils on enzymes involved in the eicosanoid cascade is depicted. For the 5-LOX assay, *S. album* essential oil showed a significant inhibition at the range of concentrations from 1000 to 31.25 μg mL^{-1} (1000-62.5 μg mL^{-1}, $p < 0.0001$; 31.25 μg mL^{-1}, $p < 0.05$). *S. spicatum* essential oil showed activity at the range of concentrations 1000-62.5 μg mL^{-1} ($p < 0.0001$). The calculated IC_{50} values were 82.29 ± 8.85 μg mL^{-1} and 121.33 ± 52.03 μg mL^{-1} respectively. For the PLA_2 assay, *S. album* showed significant differences with the untreated control at the two highest concentrations tested 250 μg mL^{-1} ($p < 0.001$) and 125 μg mL^{-1} ($p < 0.01$). *S. spicatum* showed a broader range of significantly active concentrations from 62.5 μg mL^{-1} ($p < 0.05$) to 500 μg mL^{-1} ($p < 0.0001$). Still, *S. album* displayed a lower IC_{50} value (100.12 ± 41.36 μg mL^{-1}) than the one for *S. spicatum* (114.21 ± 17.25 μg mL^{-1}). Regarding COX inhibition, only the results for *S. spicatum* are presented in Fig. 3. *S. album* exhibited a maximum inhibition of only 27% across the same range of concentrations tested; therefore, the results are not shown. *S. spicatum* significantly inhibited COX-2 enzyme ($p < 0.01$) at the two highest concentrations 62.5 μg mL^{-1} and 31.25 μg mL^{-1}. The essential oil also inhibited COX-1 at the highest concentration (62.5 μg mL^{-1}) while showing no significant differences at 31.25 μg mL^{-1}. Regarding tyrosinase inhibitory activity (data not shown), neither essential oil reached the IC_{50} within the concentration range tested. At the highest concentration evaluated (500 μg mL^{-1}), *S. spicatum* essential oil showed 50.71% tyrosinase inhibition, whereas *S. album* essential oil exhibited 45.33% inhibition.

3.6. Toxicity in Artemia salina

The toxicity of both essential oils was also evaluated using adult *A. salina*. No decrease in *Artemia salina* survival was at the concentrations evaluated (Fig. 4). The LD_{50} values for both essential oils could not be determined.

4. Discussion

Traditional medicinal systems have long used sandalwood (*Santalum* spp.) to treat a wide range of health conditions, including various skin disorders. Scientific interest in this plant has grown in recent years, leading to the investigation of its bioactive properties. These studies have not only helped to validate some of its traditional uses but have also resulted in the incorporation of sandalwood and its essential oils into modern therapeutic formulations (Busse et al., 2014; Edelkamp et al., 2023; Roopesh et al., 2023).

In this study, the chemical profiles of the essential oils from both *S. album* and *S. spicatum* were determined and found to be consistent with those reported in previous studies. Regarding *S. album*, (Z)-α-santalol and (Z)-β-santalol were the predominant compounds, with relative

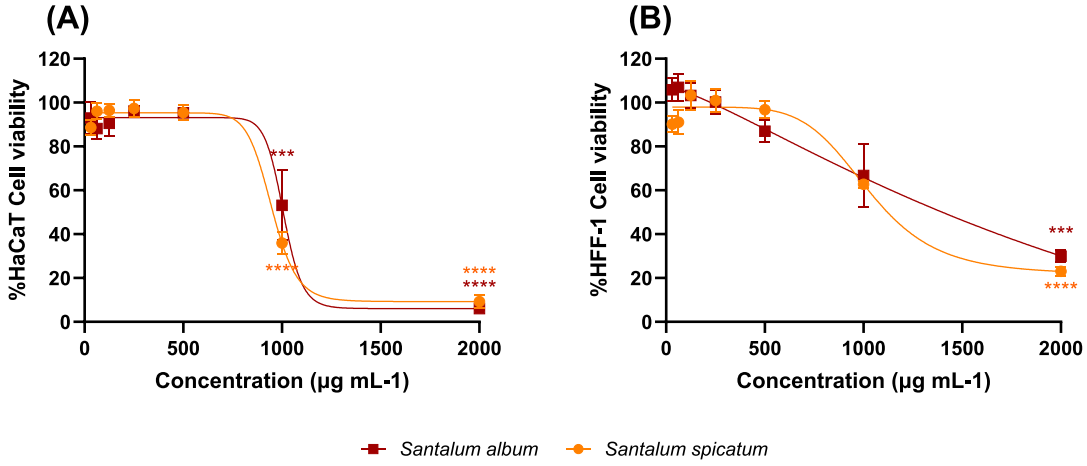

Fig. 1. Impact of *Santalum album* and *Santalum spicatum* essential oils on HaCaT and HFF-1 cells. (A) Impact of the essential oils on HaCaT keratinocytes. (B) Effects of the essential oils on HFF-1 fibroblasts. Concentrations from 500 μg mL^{-1} to 31.25 μg mL^{-1} are non-cytotoxic, whereas exposure up to 1000 and 2000 μg mL^{-1} was assayed to calculate the CC_{50}. Results are presented as mean ± SEM. At least three independent assays were performed. Statistical significance was assessed using one-way ANOVA. Statistical significance is indicated as *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$.

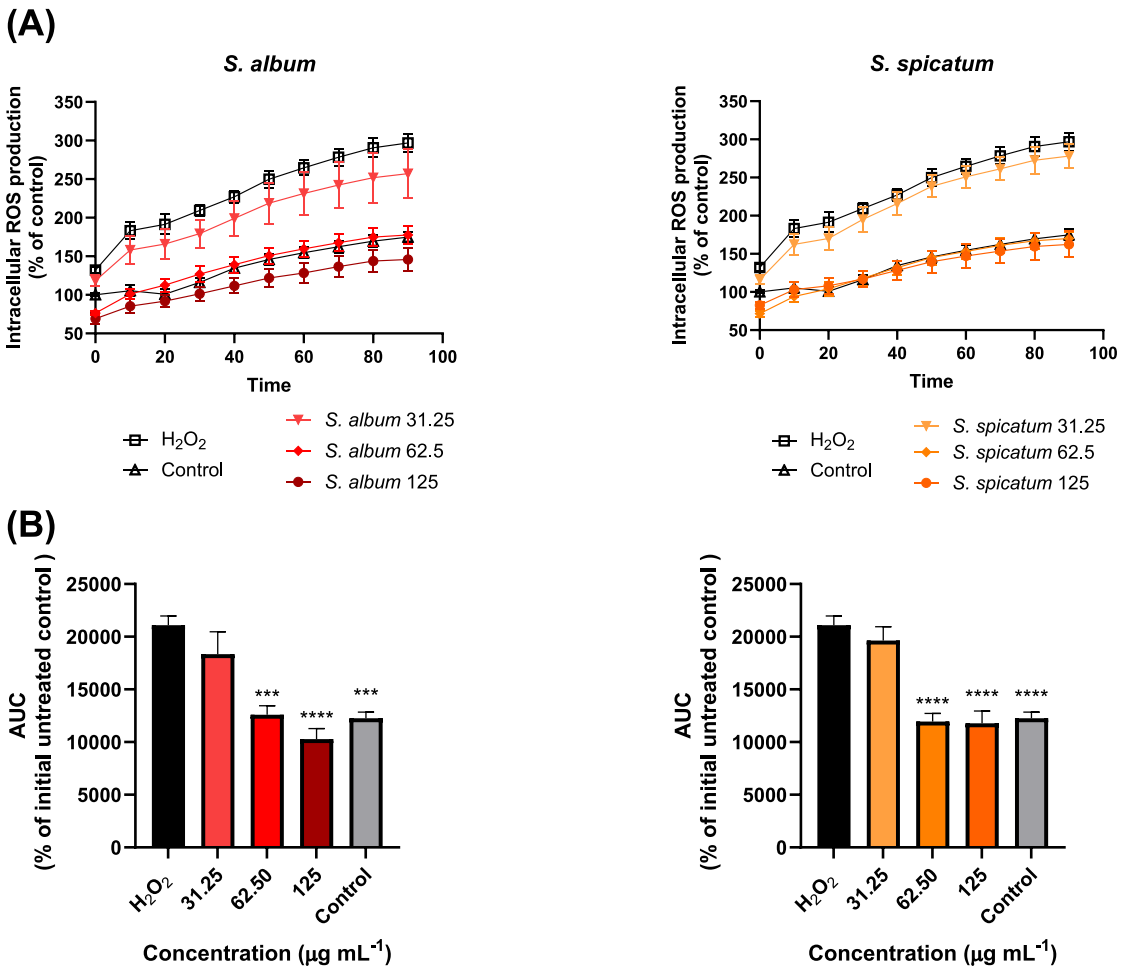

Fig. 2. Effect of essential oils on ROS production in H_2O_2-stressed HaCaT cells. (A) Intracellular reactive oxygen species (ROS) production in HaCaT cells exposed to H_2O_2 (500 µM) and treated with different concentrations of *S. album* and *S. spicatum* essential oils. ROS levels were monitored over time and expressed as a percentage relative to the untreated control at the initial time point, which was set as 100%, allowing visualization of the temporal evolution of ROS production. (B) Quantification of the overall ROS response by area under the curve (AUC) analysis. Data are presented as mean ± SEM from at least three independent experiments. Statistical significance is indicated as $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, and $****p < 0.0001$.

Table 3
MBC/MIC ratio used to determine whether the essential oils exhibited bacteriostatic or bactericidal activity, and selectivity index (SI). The MBC/MIC ratio was calculated by dividing the MIC by the MBC. Ratios ≤ 4 were considered bactericidal, whereas ratios > 4 were considered bacteriostatic. A selectivity index was determined by dividing the CC_{50} value by the MIC. SI ≥ 10 was considered good selectivity; SI values between 1 and 10 indicate moderate selectivity; SI ≤ 1 indicates lack of selectivity, with cytotoxicity comparable to or greater than antimicrobial activity.

		Santalum album			*Santalum spicatum*		
		MBC/MIC	SI (CC_{50}/MIC) (HaCaT)	SI (CC_{50}/MIC) (HFF-1)	MBC/MIC	SI (CC_{50}/MIC) (HaCaT)	SI (CC_{50}/MIC) (HFF-1)
Streptococcus agalactiae	Diabetic foot	2	28.52	41.87	1	29.93	38.96
Streptococcus anginosus	Surgical wound	1	57.04	83.75	2	29.93	38.96
Staphylococcus lugdunensis	Otic	2	28.52	41.87	4	14.96	19.48
Staphylococcus aureus [a]	Non-surgical wound	4	28.52	41.87	4	29.93	38.96
Staphylococcus aureus	Exudate	2	14.26	20.94	1	14.96	19.48
Staphylococcus aureus [b]	Non-surgical wound	2	14.26	20.94	2	14.96	19.48
Staphylococcus aureus	Ulcer	2	14.26	20.94	2	14.96	19.48

[a] Oxacilin susceptible.
[b] Oxacilin resistant; SI: selectivity index.

abundances of approximately 48% and 22%, respectively, in agreement with previous reports (Han et al., 2017). The chemical composition found in our study is also consistent with that reported by Mohankumar et al. (2019), who identified α-santalol (41.77%) and β-santalol (18.02%) as the major constituents of the essential oil (Mohankumar et al., 2019). The chemical composition reported in this work meets

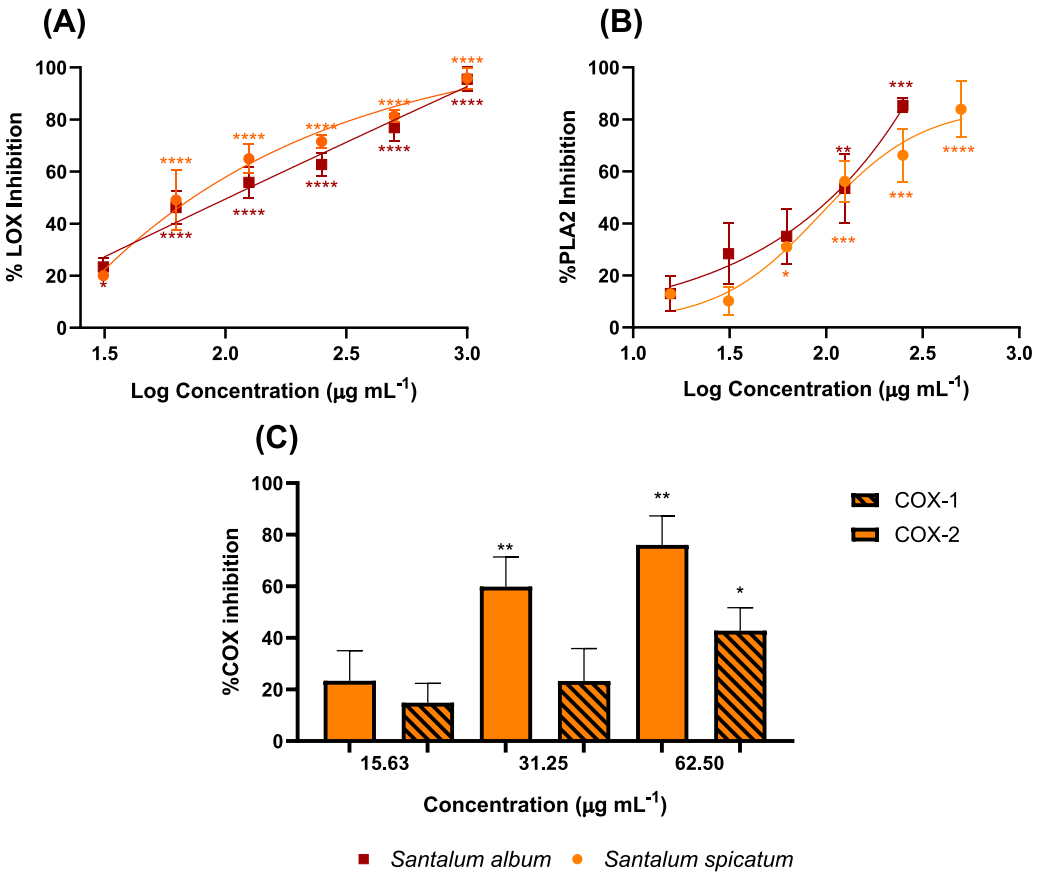

Fig. 3. Inhibition of 5-LOX, PLA2 and COX enzymes by *S. album* and *S. spicatum* essential oils. (A) Shows the inhibition of 5-LOX. (B) Shows the inhibition of PLA2. (C) Shows only the effect of *Santalum spicatum* essential oil on COX-1 and COX-2. Results were normalized to the untreated control (not shown). Quercetin was used as a positive control for 5-LOX, displaying and IC_{50} of 7.24 ± 2.95 µg mL^{-1}. Thioetheramide-PC was used as a positive control for PLA2, displaying an inhibition of 80.61 ± 4,87% at 100 µM. Manufacturer of COX kit did not provide a positive control. Values are presented as mean ± SEM from at least three independent experiments. Statistical significance was assessed using one-way ANOVA followed by Dunnett's post hoc correction for multiple comparisons (statistical significance: *$p < 0.05$; **$p < 0.01$. ***$p < 0.001$. ****$p < 0.0001$).

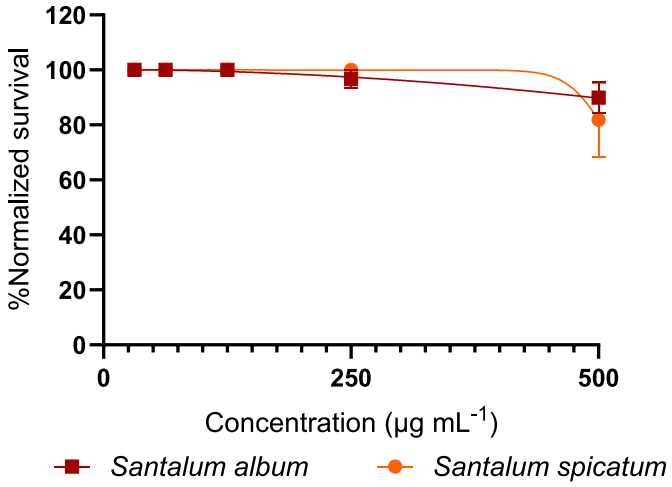

Fig. 4. Toxicity of *S. album* and *S. spicatum* on adult *A. salina*. Survival of adults after 24 h exposure to both essential oils (500–31.25 µg mL^{-1}) in seawater. Mortality was determined by counting dead individuals among groups of ten organisms per condition after 24 h. Results represent survival percentages corrected for natural mortality in the untreated control. Values are presented as mean ± SEM. At least three independent assays were performed. Statistical significance was assessed using one-way ANOVA. Statistical analysis revealed no significant differences.

the requirements of the ISO 3518:2025, which indicated that the acceptable range of α-santalol and β-santalol is 41–55 and 16–27%, respectively (International Organization for Standardization, 2025; Kucharska et al., 2021).

Conversely, essential oils derived from *S. spicatum* are often considered of lower value compared with those from *S. album*, owing to their reduced santalol content and the greater diversity of sesquiterpene constituents (Brand and Pronk, 2011; Yan et al., 2024). The chemical composition determined in this study is consistent with that previously reported in the literature. For instance, Shellie et al. (2004) reported a (*Z*)-α-santalol and (*Z*)-β-santalol content of 22 and 5.2%. On the contrary, the content of (*Z*)-nuciferol (18.4%) found in our study is significantly higher than that previously reported (2.8%) (Shellie et al., 2004). The chemical composition of the essential oils can vary according to different factors, as plant geographic origin, collection time, or storage conditions of the plant material. Although the overall chemical composition observed in this study was consistent with previous reports, minor differences in the relative abundance of individual compounds may be attributed to factors such as the geographical origin of the plant material, harvesting time, storage conditions, and natural batch-to-batch variability. Therefore, compositional differences between batches should be taken into account when comparing the chemical profiles of commercially available essential oils across different studies.

In this work, both essential oils tested showed antibacterial activities against the Gram-positive isolates from diabetic foot infections, surgical and non-surgical wounds, otic samples, exudates, and ulcers. Santalol

has previously been shown to possess antimicrobial properties, and the presence of this compound may explain the observed activity (Jirovetz et al., 2006). However, despite the previously mentioned differences in the santalol amount, both essential oils showed similar MIC values for some of the bacterial isolates such as *S. agalactiae* and *S. aureus*. This suggests that minor compounds present at higher relative abundances in *S. spicatum* may also contribute to its antibacterial activity. Bisabolol, a sesquiterpene alcohol identified in the *S. spicatum* essential oil tested herein, has previously shown antimicrobial activity against *S. aureus* and synergistic or modulatory effects when combined with different antibiotics, including effects associated with bacterial efflux pumps (da Cruz et al., 2020; Eddin et al., 2022; Gnankiné and Bassolé, 2017; Rodrigues et al., 2018). Similarly, nerolidol has demonstrated antibacterial and antibiofilm activity against *S. aureus*, together with membrane-permeabilizing and antibiotic-potentiating effects, suggesting that even moderate amounts of this compound could contribute to the overall antibacterial effect of the oil (de Moura et al., 2021; Santana et al., 2023). Farnesol, another sesquiterpene alcohol detected in *S. spicatum*, has also shown relevant activity against *S. aureus*, including disruption of membrane integrity, inhibition of biofilm formation, and enhancement of susceptibility to antimicrobial agents (Inoue et al., 2016; Ivanova et al., 2022; Kaneko et al., 2011; Lopes et al., 2021). In contrast, although α- and β-santalol are among the characteristic constituents of sandalwood oils, evidence for their direct antibacterial activity as isolated compounds against *Staphylococcus* spp. remains comparatively limited, and much of the available antimicrobial evidence derives from whole sandalwood oils. Therefore, the contribution of non-santalol constituents, particularly sesquiterpene alcohols such as α-bisabolol, nerolidol, and farnesol, should not be overlooked and may partly explain the similarities observed in antibacterial activity despite differences in santalol content between the oils.

The antibacterial activity was observed against several clinically relevant Gram-positive isolates, encompassing bacterial species associated with a range of human infections. *S. aureus* is a major pathogen associated with skin, soft tissue, and wound infections, with methicillin-resistant strains further complicating their clinical management (Hatlen and Miller, 2021; Turner et al., 2019). In this study, both essential oils demonstrated antimicrobial activity against this pathogen, consistent with previous reports (Xiao et al., 2020). One previous study even described that when used as a dietary additive, sandalwood significantly enhanced the resistance of tilapia to *S. aureus* infection by modulating the immune response and reducing inflammation (Mansour et al., 2024).

On the other hand, *S. anginosus* are mucosal commensals but have been implicated in abscess-forming infections. In contrast, *S. lugdunensis* is a common cause of community-acquired skin infections, typically presenting with purulent lesions (Pilarczyk-Zurek et al., 2022). *S. agalactiae* is traditionally recognized as a perinatal pathogen; however, it has also been isolated from diabetic wound infections. Strains recovered from these chronic wounds are often challenging to manage, partly due to their elevated levels of antimicrobial resistance. In addition, Group B Streptococcus, including *S. agalactiae*, induces pro-inflammatory responses that contribute to the persistence of the chronic wound microenvironment (Keogh et al., 2022; Keogh and Doran, 2023). To our knowledge, the effects of neither *S. album* nor *S. spicatum* on these bacteria have been previously investigated. Given their clinical importance of these bacteria, the observed bactericidal activity of the essential oils underscores their potential as promising therapeutic candidates. However, future studies including a larger number of clinical isolates, particularly additional methicillin-resistant *S. aureus* isolates, as well as biofilm-forming strains, would be valuable to confirm and further characterize the antibacterial activity observed in the present study, especially considering the relevance of biofilms in chronic wound infections.

The results obtained for Gram-positive bacteria are particularly noteworthy, whereas no relevant activity was observed against the Gram-negative isolates tested (MIC $>$ 1000 μg mL^{-1}). Although the antibacterial mechanism of sandalwood essential oil has not yet been fully elucidated, the lipophilic nature of its major constituents, particularly α- and β-santalol, suggests that interaction with bacterial membranes may contribute to its activity. Incorporation of hydrophobic compounds, such as those found in essential oils, into the lipid bilayer may alter membrane integrity and permeability, disrupt cellular homeostasis, and ultimately lead to irreversible cell damage, which would be consistent with the bactericidal effect observed in the present study (Swamy et al., 2016). The greater susceptibility of Gram-positive isolates observed here could also be related to differences in cell envelope architecture, as the outer membrane of Gram-negative bacteria may constitute an additional barrier to the penetration of hydrophobic compounds (Angane et al., 2022). However, the limited number of Gram-positive and Gram-negative isolates included in this study precludes drawing firm conclusions regarding an association between cell envelope structure and susceptibility to sandalwood essential oils. Furthermore, previous studies have reported activity of sandalwood essential oils and *S. album* extracts against Gram-negative bacteria (Jirovetz et al., 2006; Khan et al., 2013; Misra and Dey, 2012), indicating that additional factors, such as essential oil composition, bacterial strain, or methodological differences, may influence antibacterial activity. Therefore, while the present findings are consistent with a possible membrane-related mechanism of action, dedicated mechanistic studies, such as time-kill assays and membrane disruption analyses, would be required to confirm this hypothesis. Interestingly, both essential oils exhibited bactericidal activity against the susceptible strains, as indicated by MBC/MIC ratios $\leq$ 4 (Ishak et al., 2024), a finding that could be consistent with substantial membrane perturbation leading to irreversible cellular damage. Nevertheless, this interpretation remains hypothetical, as membrane integrity or permeability was not directly assessed in the present study.

The ecotoxicity assay using adult *A. salina* indicated that no significant toxic effects were observed at concentrations of 500 μg mL^{-1} and below. Notably, the MIC and MBC values previously determined for the essential oils against the tested bacterial strains lie within concentrations that do not elicit significant toxic effects. These results suggest that the antimicrobial activity of the essential oils occurs at concentrations that do not produce toxicity in the *A. salina* model. Furthermore, the LD_{50} could not be calculated within the range of concentrations tested, indicating relatively low acute toxicity under the experimental conditions. In addition, selectivity index values, calculated by comparing the MIC with the CC_{50} in mammalian cells, were higher than 10, indicating a favourable balance between antimicrobial activity and cytotoxicity (Indrayanto et al., 2021; Kumar et al., 2024). Although these results support a favourable safety profile in HaCaT and HFF-1 cells, this index only reflects general cellular cytotoxicity and does not assess other relevant dermatological endpoints, such as skin irritation, allergic contact dermatitis, or sensitization, which may be associated with essential oils and some of their individual constituents (Geier et al., 2022). Therefore, these findings provide a useful initial indication of biocompatibility, but additional studies specifically addressing dermal irritation and sensitization are required to establish a more comprehensive dermatological safety profile.

Still, not only did the essential oils appear to be non-cytotoxic, but they also reduced ROS production at low, non-cytotoxic concentrations. This finding is particularly relevant in keratinocytes, as excessive ROS accumulation can promote oxidative stress, cellular damage, and the activation of signalling pathways involved in cutaneous inflammation and skin disorders. Therefore, the observed reduction in intracellular ROS suggests that, at non-cytotoxic concentrations, these essential oils may exert an additional protective effect against oxidative stress in epidermal cells. This aligns with previous studies have also investigated various formulations incorporating sandalwood in different forms, including synthetic analogues, biomaterial-derived components, or oil-loaded scaffolds, highlighting its beneficial effects on skin and wound-healing–associated responses (Busse et al., 2014; Mujawar et al., 2025;

Roopesh et al., 2023). Nevertheless, further studies using oxidative stress-induced models and additional oxidative damage and inflammatory markers would be required to confirm a potential antioxidant or skin-protective effect.

In addition, the reduction in intracellular ROS observed in HaCaT keratinocytes may contribute to an anti-inflammatory effect, since excessive ROS can act as signalling mediators that promote the activation of inflammatory pathways. In HaCaT cells, ROS scavenging has been shown to reduce NF-κB activation and the production of pro-inflammatory mediators such as IL-6 and IL-8, while ROS generation can also promote NLRP3 inflammasome activation and IL-1β release (Cho et al., 2012; Yang et al., 2011).

Inflammation is essential for defending the host against pathogens, but excessive or uncontrolled responses can damage tissues and worsen disease. In many infections, tissue injury results more from prolonged immune activation and cytokine release than from the pathogen itself. Previous works have pointed out the anti-inflammatory properties of sandalwood essential oils, focusing on the regulation of pathways such as SKN-1/Nrf2 and NF-κB, inhibition of pro-inflammatory cytokines, and suppression of phosphodiesterase (PDE) activity (Lee et al., 2021; Mohankumar et al., 2018; Sharma et al., 2014, 2017, 2018). In the present study, in addition to evaluating their effects on ROS production, we investigated the direct *in vitro* inhibitory effects of *S. album* and *S. spicatum* essential oils on key enzymes involved in the eicosanoid cascade. The results show that both essential oils inhibit 5-LOX and PLA_2. However, for the COX inhibition *S. spicatum* showed greater inhibition values at the same concentrations tested. The essential oil inhibited both COX-2 and COX-1 enzymes, although it showed less activity for the latest one. COX-1 is constitutively expressed in most tissues and is primarily involved in physiological homeostasis, including gastric mucosal protection, maintenance of renal perfusion, and regulation of platelet aggregation through thromboxane A_2 (TXA_2) production. In contrast, COX-2 is largely inducible and upregulated during inflammatory processes. For this reason, preferential inhibition of COX-2 over COX-1 is generally considered desirable, although selective COX-2 inhibition has been associated with an increased cardiovascular risk (Koshman et al., 2023; Nissen et al., 2016; Saad and Pellegrini, 2025). Therefore, the results of *S. spicatum* essential oil which showed greater inhibition of COX-2 than COX-1 are of interest. Nevertheless, additional studies are required to determine the relevance of this inhibitory activity. In addition, further cell-based studies evaluating specific inflammatory mediators, such as interleukin production or the expression of inflammation-related markers, would be required to complement the present findings and to better characterize the cellular pathways potentially involved in the observed effects.

From a pharmacological standpoint, *S. spicatum* and *S. album* targeting several enzymes of the eicosanoid cascade is worth to highlight since they seem to interfere with the arachidonic acid cascade at multiple levels, potentially reducing both prostanoid and leukotriene generation. In particular, concomitant COX and 5-LOX inhibition may help prevent metabolic shunting toward leukotriene synthesis that has been described following isolated COX inhibition, a phenomenon associated with increased cysteinyl-leukotriene production in susceptible individuals (Bobolea et al., 2023; Christie et al., 1991; Laidlaw, 2018). Given the contribution of leukotrienes to bronchoconstriction, vascular permeability, and leukocyte recruitment, their simultaneous modulation may be relevant in inflammatory conditions where both prostaglandins and leukotrienes are involved.

5. Conclusions

Regardless of the differences observed in santalol levels, both essential oils were effective against the Gram-positive clinical isolates tested, exerting bactericidal activity (MBC/MIC<4) against *S. aureus* (including oxacillin-resistant isolates), *S. agalactiae*, *S. anginosus*, and *S. lugdunensis*. MIC values ranged from 15.625 to 62.5 μg mL^{-1}, while MBC values ranged from 31.25 to 125 μg mL^{-1}. Importantly, selectivity indices calculated from MIC and CC_{50} values obtained from HaCaT and HFF-1 cells were greater than 10, indicating favourable selectivity toward bacterial cells over mammalian cells. In addition to their antimicrobial effects, both essential oils modulated key enzymes of the eicosanoid pathway, with *S. spicatum* being particularly noteworthy due to its impact on COX-2 activity. Taken together, these findings are consistent with the traditional use of *Santalum* species in the context of infectious and inflammatory skin conditions and provide further basis for investigating their ethnopharmacological relevance. Overall, these findings demonstrate *in vitro* antibacterial and enzyme-inhibitory activities of *S. album* and *S. spicatum* essential oils and provide a basis for further investigation of their biological properties. Additional studies, including skin-relevant models, mechanistic approaches, and *in vivo* or *ex vivo* evaluations, are required to determine their potential relevance for dermatological applications.

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CRediT authorship contribution statement

Pilar Cebollada: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **Eleonora Spinozzi:** Investigation, Writing – review & editing. **Elena Alvarado:** Investigation, Writing – review & editing. **Cristina Seral:** Conceptualization, Resources, Supervision, Writing – review & editing. **Riccardo Petrelli:** Writing – review & editing. **Filippo Maggi:** Methodology, Resources, Supervision, Writing – review & editing. **Víctor López:** Conceptualization, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jep.2026.122262.

Data availability

Data will be made available on request.

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