

Synergistic Antibacterial Activity of the Combination Limonene and Salicylic Acid Against *Staphylococcus aureus* in Atopic Dermatitis

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Received: November 25, 2025

Revised: August 15, 2026

Accepted: September 21, 2026

Published: September 30, 2026

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DOI: [10.29303/jppipa.v12i9.13590](https://doi.org/10.29303/jppipa.v12i9.13590)

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Abstract: Atopic dermatitis increases susceptibility to *Staphylococcus aureus* colonization, while increasing antibiotic resistance underscores the need for alternative antibacterial agents. This study provides antimicrobial activity and synergistic potential of limonene and salicylic acid—two essential oil components commonly found in Indonesian plants—against *S. aureus* ATCC 25923. The antibacterial effect was measured using the inhibition zone diameter (IZD) and minimum inhibitory concentration (MIC) assays. Limonene produced the largest inhibition zone at a concentration of 400–500 mg/mL, while salicylic acid showed optimal inhibition at 100 mg/mL. The combination of the two with a 1:9 ratio produced the largest inhibition zone of 20.35 mm, with the volume ratio significantly affecting the IZD value ($P < 0.001$). The MIC results showed that limonene and salicylic acid had MIC values of 62.5 mg/mL and 6.25 mg/mL, respectively. The 1:9 combination substantially reduced the MIC to 0.12 mg/mL (0.01 mg/mL limonene and 0.11 mg/mL salicylic acid). A FICI value of 0.01 indicates a very strong synergistic effect ($FICI \leq 0.5$). Overall, the combination of limonene and salicylic acid demonstrated significantly enhanced antibacterial activity compared to the individual compounds, supporting their potential as a synergistic alternative natural antibacterial for managing *S. aureus*-associated skin infections.

Keywords: Antimicrobial activity; Limonene; Salicylic acid; *Staphylococcus aureus*; Synergistic effect

Introduction

Atopic dermatitis (AD) or eczema is a chronic skin disease characterized by skin barrier damage, inflammation, persistent itching (pruritus), and microbial dysbiosis, with *Staphylococcus aureus* playing a key role in its pathogenesis (Bai et al., 2025; Özdemir & Öksüz, 2024; Wang et al., 2024b; Aurelly & Santoso, 2023). In the 21st century, the 1-year prevalence of doctor-diagnosed AD ranged from 1.2% in Asia to 17.1% in Europe in adults, and 0.96% to 22.6% in children in Asia (Bylund et al., 2020). Data collected between January 2022 and December 2023 from reports of 13

Dermatology and Venereology polyclinics at teaching hospitals affiliated with specialist medical education institutions in Indonesia recorded 243 cases (0.9%) of atopic dermatitis in children and 223 cases (0.86%) in adults, out of a total of 25,930 new patients (Perhimpunan Dokter Spesialis Kulit dan Kelamin Indonesia, 2024).

The etiology of atopic dermatitis is highly complex, involving both genetic and environmental factors (Schuler et al., 2024). One of the major genetic contributors is mutation in the FLG gene, which disrupts filaggrin production and damages the protective function of the skin (Baidya & Mabalirajan, 2025;

How to Cite:

A'yun, Q., Aprianie, W., Astuti, R. W., & Laura, A. P. P. (2026). Synergistic Antibacterial Activity of the Combination Limonene and Salicylic Acid Against *Staphylococcus aureus* in Atopic Dermatitis. *Jurnal Penelitian Pendidikan IPA*, 12(9), 169–175. <https://doi.org/10.29303/jppipa.v12i9.13590>

Stefanovic & Irvine, 2024). Consequently, the skin becomes more susceptible to colonization by microorganisms such as *Staphylococcus aureus* (Wang et al., 2024b), which can aggravate symptoms and increase the risk of systemic infection (Napolitano et al., 2025; Stefanovic & Irvine, 2024).

S. aureus is a Gram-positive bacterium commonly found on the skin, but it can become a dangerous pathogen in individuals with atopic dermatitis or weakened immune systems (Delanghe et al., 2024; Deng et al., 2023). This increased susceptibility is closely linked to filaggrin (FLG) deficiency, which disrupts skin barrier integrity and reduces the production of natural moisturizing factor (NMF). Under these conditions, the bacteria can proliferate and transmit virulence factors, including the production of toxins such as V8 protease and phenol-soluble modules (PSMs), which activate inflammation, degrade epidermal components, and promote biofilm formation, thus increasing resistance to treatment (Chung et al., 2022; Deng et al., 2023; Gallo & Horswill, 2024; Grando et al., 2022).

Studies have shown that *S. aureus* has developed resistance to various β -lactam and non- β -lactam antibiotics such as erythromycin, clindamycin, gentamicin, linezolid, and tetracycline (Lade et al., 2022; Sharma et al., 2024). Although antibiotic combinations such as daptomycin and rifampicin remain in use, resistance continues to rise. An alternative approach is the use of essential oil combinations as natural antibacterial agents. Synergistic antimicrobial activity of essential oils mixture of *Moringa oleifera*, *Cinnamomum verum*, and *Nigella sativa* have demonstrated strong antimicrobial potential against *S. aureus*, in some cases exceeding the effectiveness of antibiotics like tetracycline (Abu-Hussien et al., 2025). The combination of *Thymus broussonnetii* and *Thymus pallidus* essential oils with streptomycin reportedly enhanced antibacterial activity against *S. aureus* up to eight-fold (Amassmoud et al., 2023). Similarly, cinnamon and oregano oil combinations at ratios of 8:2 and 9:1 exhibited which also showed strongly synergistic activities against *S. aureus* and *Bacillus cereus* (Nguyen et al., 2025). Moreover, the combination of *Citrus reticulata* peel oil and limonene with gentamicin showed synergistic effects against both MRSA (Methicillin-Resistant *S. aureus*) and MSSA (Methicillin-Sensitive *S. aureus*) isolates (Sreepian et al., 2022). These findings highlight the great potential of essential oil combinations as natural antibacterial agents to combat infections caused by antibiotic-resistant bacteria.

In Indonesia, research on essential oil combinations against *S. aureus* remains limited. This is noteworthy given that approximately 40 out of 99 essential oil-producing plants worldwide grow abundantly in Indonesia (Balai Pengelola Hasil Perakitan dan

Modernisasi Pertanian, 2023), with essential oil exports reaching 11,755 tons in June 2025. This situation emphasizes the importance of investing in research, innovation, and product development based on essential oils domestically, allowing Indonesia not only to serve as a raw material exporter but also as a pioneer in natural product-based health solutions.

Among essential oils that remain underexplored are citrus oil and wintergreen oil. Limonene from citrus oil has been shown to have antibacterial activity with a minimum inhibitory concentration (MIC) of 20 mL/L, primarily by disrupting bacterial cell membranes (Han et al., 2021). Meanwhile, wintergreen oil, which is rich in methyl salicylate, can be hydrolyzed to salicylic acid, the active form that plays a role in inhibiting *Staphylococcus aureus* biofilm formation (Song et al., 2022; Kumari, 2020). These differences in mechanisms of action suggest the potential for a more effective synergistic effect through a multi-target approach, namely by simultaneously targeting the cell membrane and biofilm system. Therefore, this study aims to evaluate the synergistic potential between limonene and salicylic acid as a natural antibacterial alternative for skin infections caused by *S. aureus*, and support the development of innovations based on high-value natural products derived from Indonesian essential oil resources.

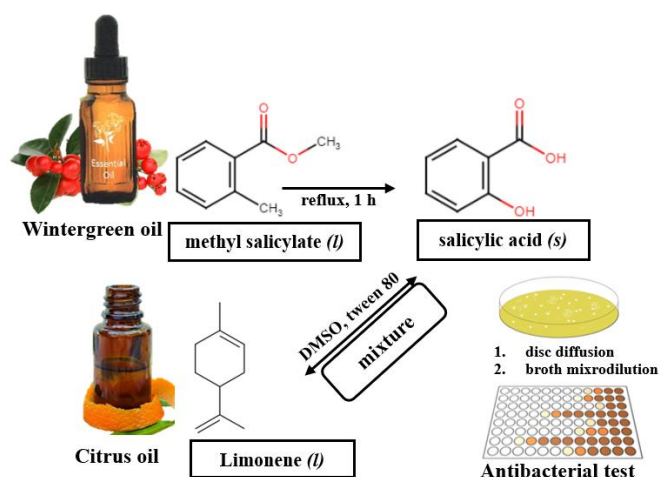


Figure 1. Evaluation of combination antibacterial activity of limonene and salicylic acid by microdilution

Method

Essential Oil Characterization

The materials used were limonene from orange oil obtained from Tetesan Atsiri, Bogor Regency using the cold pressed method and wintergreen oil sourced from PT. Wijaya Matahari Makmur, North Jakarta using the steam distillation method, then hydrolyzed to produce salicylic acid used in this study. The samples were

dissolved in approximately 8 mL of *n*-hexane and injected into a Gas Chromatography–Mass Spectrometry instrument (GC-MS) in the integrated laboratory of the Islamic University of Indonesia. GC-MS used a Rtx-5MS column (5% diphenyl/95% dimethyl polysiloxane) and Carbowax (Polyethylene glycol) with helium as the carrier gas and temperature for ion source is 200 °C and interface is 250 °C. The GC-MS analysis provided molecular weight data, fragmentation patterns, and compound predictions.

Hydrolysis of Methyl Salicylate from Wintergreen Oil

Five grams of methyl salicylate from wintergreen oil were placed into a three-neck round-bottom flask, followed by the addition of 50 mL of 5 M NaOH. The mixture was refluxed for 30 minutes with continuous stirring. The resulting solution was transferred into an Erlenmeyer flask and allowed to cool to room temperature. The solution was then placed in an ice bath while HCl was added dropwise until the pH reached 2. The precipitate obtained was filtered using a Büchner funnel and dissolved in hot water for purification.

Characterization of Hydrolysis Product

The hydrolysis product was oven-dried at 60 °C for 6 hours to ensure complete removal of residual moisture, and the resulting salicylic acid was characterized by Thin Layer Chromatography (TLC), Fourier Transform Infrared Spectroscopy (FT-IR), and melting point analysis.

Inhibitory Zone Diameter (IZD)

The antibacterial activity was evaluated using the paper disc diffusion method. *Staphylococcus aureus* ATCC 25923 was cultured in Nutrient Broth (NB) and incubated at 37 °C for 24 h. The 24-hour culture was adjusted to an optical density (OD) of 0.1 in physiological saline, and 100 µL of the suspension was spread onto Mueller Hinton Agar (MHA) plates. Each test sample (20 µL) was applied to sterile blank discs (5 mm diameter). The plates were incubated at 37 °C for 24 h, and the inhibition zones around the discs were measured using a caliper.

Determination of Minimum Inhibitory Concentration (MIC)

MIC tests of limonene, salicylic acid, and combination compounds were carried out at concentrations that produced optimal inhibition zones using the serial microdilution method. A serial concentration of limonene ranging from 500 to 0.488 mg/mL and salicylic acid ranging from 100 to 0.0976 mg/mL was prepared. The combination compounds were prepared using DMSO and Tween 80 as solvents. Ciprofloxacin and DMSO were used as the positive and negative controls, respectively.

Bacterial colonies from Nutrient Agar or Mueller Hinton Agar (MHA) were inoculated into 3 mL of fresh Mueller Hinton Broth (MHB) and incubated at 37 °C for approximately 3 hours until reaching the logarithmic growth phase ($OD_{600} \approx 0.1$). An OD_{600} value of 0.1 corresponds to approximately 0.5 McFarland standard or 1.5×10^8 CFU/mL.

Subsequently, 100 µL of the standardized suspension ($OD_{600} = 0.1$) was added to 10 mL of MHB to obtain a working suspension with a bacterial density of approximately 10^6 CFU/mL. This suspension was used as the inoculum for the microplate assay.

In a 96-well microplate, 50 µL of Mueller–Hinton Broth (MHB) was added to wells in columns 1–10 for the serial dilution series. Then, 100 µL of the test compound at the highest concentration was added to column 11, while 100 µL of MHB without bacterial inoculum was added to column 12 as the sterility control. A two-fold serial dilution was performed sequentially from column 11 to column 2 by transferring 50 µL between wells. After mixing, 50 µL was discarded from column 2 to ensure that each well contained 50 µL prior to inoculation. The bacterial suspension was prepared by diluting an initial suspension ($\approx 1 \times 10^8$ CFU/mL) into fresh medium to obtain a working concentration of approximately 1×10^6 CFU/mL. Subsequently, 50 µL of this bacterial suspension was added to each well in columns 1–11, resulting in a final volume of 100 µL per well. Column 12 was left uninoculated. The microplate was incubated at 37 °C for 18–24 hours. Bacterial growth was assessed by measuring the optical density at 600 nm (OD_{600}) using a microplate reader. The minimum inhibitory concentration (MIC) was defined as the lowest concentration of the test compound that showed no visible bacterial growth (clear well).

Fractional Inhibitory Concentration Index (FICI) Analysis

The FICI of limonene and salicylic acid combined was calculated to evaluate their interactions against resistant bacterial strains. The FICI was calculated using the following formula: $FICI = (MIC \text{ of limonene and salicylic acid combination} / MIC \text{ single compound})$. The concentrations of limonene and salicylic acid combined were expressed in mg/L for consistency, with FICI values interpreted as follows: $FICI \leq 0.50$ indicates synergy, $0.50 < FICI \leq 1.00$ is additive, $1.00 < FICI \leq 4.00$ indicates indifference, and $FICI > 4.00$ suggests antagonism.

Result and Discussion

Chemical Composition of EOs

The chemical composition of the essential oils (EOs) is presented in Table 1. In sweet orange oil, the major active compound was limonene (99.22%). In

wintergreen oil, the main component was methyl salicylate (87.28%). Additionally, a compound tentatively identified as 1,2-benzenedicarboxylate was detected. However, because this compound is widely known as a contaminant derived from plasticizers, it is not considered representative of the natural composition of essential oils.

Table 1. Compound components in Sweet Orange Oil (SO) and Wintergreen Oil (WO) using GC-MS

Eos	Compound	% of total	Retention time (min)
SO	cis-Ocimene	0.19	2.96
	Sabinene	0.08	3.37
	β-Myrcene	0.45	3.53
	Octanal	0.01	3.66
	Trans-β-Ocimene	0.02	3.80
	Limonen	99.22	4.09
	Cis-Limonen Oxide	0.02	5.42
WO	Methyl salicylate	87.28	6.37
	1,2-Benzenedicarboxylic acid	12.72	11.66

Characterization of Salicylic Acid

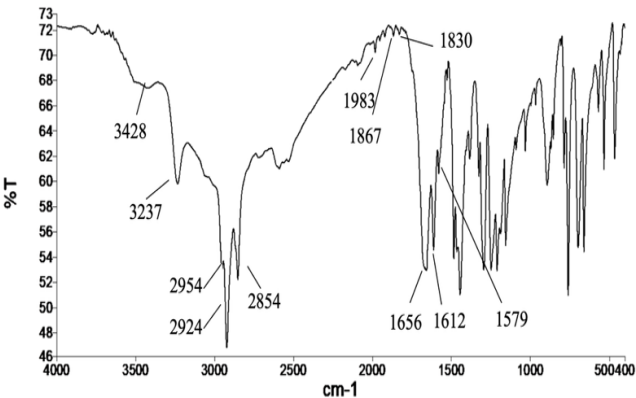
Methyl salicylate is an aromatic ester compound that serves as the main constituent of wintergreen oil and is widely known as a precursor to salicylic acid. Before testing on *Staphylococcus aureus*, this compound is first converted to its active form, salicylic acid, through a base hydrolysis reaction (saponification) using NaOH as the reactant. This reaction involves the cleavage of the ester bond through the nucleophilic attack of the hydroxide ion (OH⁻) on the carbonyl group of methyl salicylate, resulting in sodium salicylate and methanol as intermediate products. The resulting sodium salicylate is acidified by adding a strong acid, such as HCl or H₂SO₄, to lower the pH of the environment and precipitate free salicylic acid. This acidification step is crucial for converting the sodium salt into its non-ionized acid form, thus facilitating the isolation process and increasing the relevance of biological compounds in antibacterial activity testing (Özokan et al., 2024).

The obtained salicylic acid exhibited needle-shaped white crystalline characteristics (Wang et al., 2024a; Aljamal et al., 2018), as shown in Figure 2(a). The FT-IR analysis results of salicylic acid are presented in Figure 2(b). The FT-IR spectrum showed a characteristic vibration at 3428 cm⁻¹ corresponding to the O-H stretching band. Absorption bands at 2954, 2924, and 2854 cm⁻¹ were identified as C-H stretching vibrations. The asymmetric stretching of the C=O group was observed at 1656-1612 cm⁻¹, while the absorption at 1612-1579 cm⁻¹ was attributed to C=C vibrations in the phenolic ring. Additionally, the absorption bands at 1983-1830 cm⁻¹ indicated overtone patterns typical of an ortho-substituted aromatic ring. The obtained FT-IR

spectrum was consistent with that of pure salicylic acid reported in previous studies (Younis & Hussein, 2024).



(a)



(b)

Figure 2. (a) Salicylic Acid and; (b) FT-IR Spectrum of Synthesized Salicylic Acid

The melting point test using a melting point apparatus showed that the synthesized salicylic acid melted at 157.8 °C, which is close to the melting point of pure salicylic acid (158 °C) (Wang et al., 2023; Macario et al., 2024). Based on these results, it can be concluded that salicylic acid was successfully synthesized through the hydrolysis process.

Antibacterial activity of Limonene and Salicylic Acid

The IZD and MIC values of the single compounds and the combination of limonene and salicylic acid were determined to evaluate their antimicrobial activity against *Staphylococcus aureus* ATCC 25923. The IZD values differed significantly between limonene and salicylic acid. Limonene showed the highest inhibition zone at concentrations of 400-500 mg/mL, while salicylic acid exhibited the highest inhibition zone at 100 mg/mL. The combination of limonene and salicylic acid (1:9) produced the largest inhibition zone of 20.35 mm. Changes in the volume ratio between limonene and

salicylic acid significantly affected the IZD values ($P < 0.001$). The obtained IZD values were used as a reference for determining the MIC using the microdilution method.

Table 2. Inhibitory zone diameter and MIC of Limonene (L) and Salicylic Acid (SA) compounds against *Staphylococcus aureus* ATCC 25923

SA (mg/mL)	IZD (mm)	L (mg/mL)	IZD (mm)
5	6.14	15	0
10	7.09	20	0
15	7.57	25	6.75
20	7.36	30	7.3
25	7.81	60	7.55
30	7.88	80	8.37
60	16.8	100	8.83
80	17.95	100	8.97
100	18.7	200	10.04
-	-	300	12.5
-	-	400	16.56
-	-	500	17.2
K+ (ciprofloxacin 0.1 mg/mL)	33.32	-	-
K- (DMSO)	0	-	-
MIC SA	6.25 mg/mL	MIC L	62.5 mg/mL

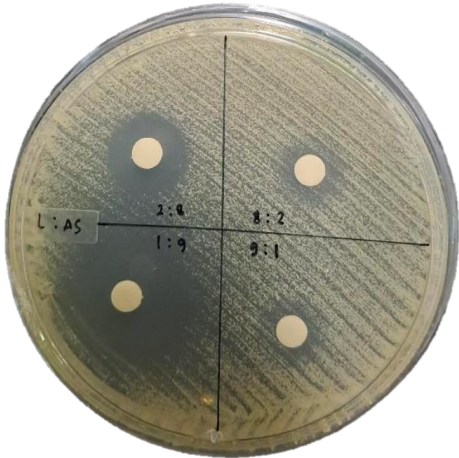
Minimum Inhibitory Concentration (MIC)

Table 3. Inhibitory zone diameter and MIC of the combined compound limonene: Salicylic Acid (L: SA)

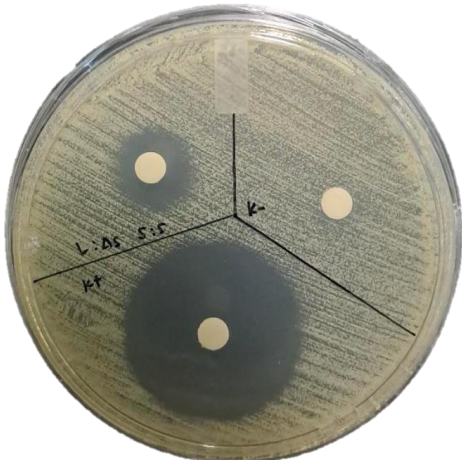
L:SA (v:v, mg/mL)	IZD (mm)	MIC (mg/mL)
2:8	13.11	
8:2	6	
1:9	20.35	0.12
9:1	0	
3:7	10.19	
7:3	6.48	
4:6	8.6	
6:4	8.6	
5:5	10.05	
p-value		<0.001

The MIC (Minimum Inhibitory Concentration) values of the single compounds showed that limonene had an MIC of 62.5 mg/mL, while salicylic acid had an MIC of 6.25 mg/mL against the tested bacteria. In the combination test of limonene and salicylic acid at a ratio of 1:9, the MIC value of the combination was 0.12 mg/mL, consisting of 0.01 mg/mL limonene and 0.11 mg/mL salicylic acid. The calculated Fractional Inhibitory Concentration Index (FICI) value for the combination was 0.0182. Based on the interpretation of FICI values (≤ 0.5 indicating a synergistic effect), the combination of limonene and salicylic acid exhibited a very strong synergistic effect against the growth of *Staphylococcus aureus* ATCC 25923. Synergistic effects

were defined as $FICI \leq 0.5$, indifferent effects (no interaction) as FICI values between >0.5 and 4, and antagonistic effects as $FICI > 4$ (Phasaludeen et al., 2025).



L: SA (2:8), (8:2), (1:9), dan (9:1)



L:SA (5:5), K+ dan K-



L:SA (3:7), (7:3), (4:6), dan (6:4)

Figure 3. Antibacterial test results using the disc diffusion method of the combined compound limonene; Salicylic Acid (L:SA)

Conclusion

Limonene showed the largest inhibition zone at the highest concentration of 400–500 mg/mL, while salicylic acid reached its optimal inhibition zone at 100 mg/mL. The combination of the two compounds with a 1:9 ratio resulted in the largest inhibition zone of 20.35 mm, with the volume ratio showing a significant effect on the IZD value ($p < 0.001$). In the MIC test, limonene showed an MIC of 62.5 mg/mL and salicylic acid 6.25 mg/mL, while the 1:9 combination significantly reduced the MIC to 0.06 mg/mL (0.01 mg/mL limonene and 0.06 mg/mL salicylic acid). The FICI value of 0.01 indicates a very strong synergistic effect ($FICI \leq 0.5$). Therefore, the combination of limonene and salicylic acid showed significantly increased antimicrobial activity compared to single compounds and demonstrated strong potential as a synergistic antibacterial agent against *Staphylococcus aureus* ATCC 25923.

Acknowledgments

The authors would like to express their sincere gratitude to the Kementerian Pendidikan, Kebudayaan, Riset, dan Teknologi (Kemendikbudristek) for providing research grant support through the Penelitian Dasar Pemula (PDP) Program in 2025.

Author Contributions

Q.A. contributed to the conceptualization, methodology, and all investigative work, including the characterization of essential oils using FTIR and GC-MS, hydrolysis of methyl salicylate, characterization of salicylic acid, and antibacterial as well as bacteriostatic-bactericidal testing; W.A. contributed to validation, supervision, project administration, and funding acquisition; R.W.A. and A.P.P.L. contributed to data curation, formal analysis, and visualization. All authors contributed to the writing and revision of the article and have approved the final version.

Funding

This research was funded by the Kementerian Pendidikan, Kebudayaan, Riset, dan Teknologi (Kemendikbudristek) through the Penelitian Dasar Pemula (PDP) Program 2025, grant number 67/LL11/KM/2025.

Conflicts of Interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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