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ANTIBACTERIAL POTENTIAL OF WATER FRACTIONS OF *Hermetia illucens* LARVES ON *Staphylococcus aureus* AND PREDICTION OF SKIN PERMEABILITY IN SILICO

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ABSTRACT
Hermetia illucens (Black Soldier Fly/BSF) larvae are one of the animals utilised as a decomposer of organic waste and a source of protein-rich animal feed. Its metabolites, especially alkaloids, have various pharmacological and antibacterial activities. This study evaluated the potential of BSF larval water fraction extract (FABSF) as an antibacterial agent against acne-causing Staphylococcus aureus, as well as predicting skin permeability and irritation effects. Methods included secondary metabolite screening, antibacterial test (disc method), and microbial reduction measurement by UV-Vis spectrophotometer. In silico tests were used to predict skin permeability and potential irritation by analysing descriptively. Screening results showed FABSF was positive for alkaloids (Dragendorff and Wagner tests), flavonoids, and saponins, but no polyphenols or terpenoids were detected. The disc method test showed FABSF (40%, 80%, 100%) did not form a zone of inhibition. However, absorbance measurements showed a decrease in microbial counts by 85.47%, 86.89%, and 90.79% at each concentration. In silico assays identified compounds such as Butoctamide, N-(2-Hydroxyethyl)dodecanamide, and thane; (3Z,6Z)-5-imino-N,N,3-trimethyl-8-[5-[(4-methyl-1-bicyclo[4. 1. 1]octanyl)methyl]-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrole-1-yl]nona-1,3,6,8-tetraen-4-amine suitable for topical preparations with good skin permeability and low risk of irritation.

Keywords: antibacterial; hermetia illucens; stapylococcus aureus; skin permeability

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INTRODUCTION

Indonesia is a megadiverse country with a unique and diverse biodiversity including flora and fauna, so it potentially become a great resources for bioactive compounds (Noor, 2023). *Hermetia illucens* or Black Soldier Fly (BSF) larvae are one of the resources that have the potential to be explored in relation to their benefits. In Indonesia, BSF larvae is known as a decomposer and a source of protein-rich animal feed (Asrowi & Farida, 2024), but lately research on the antibacterial activity of BSF larvae has been conducted. Previous study stated that BSF larvae extract has strong antibacterial activity against gram-negative bacteria namely *Salmonella sp*. and *Escherichia coli* (Harlystiarini et al., 2019) and *Salmonella thypimurium* and *Pseudomonas aeruginosa* (Auza et al., 2020). In addition, research conducted by Putra et al., (2022) on differences in BSF larvae feeding treatment did not significantly affect the results of the inhibition test on *Escherichia coli* bacteria. BSF larvae are known containing various bioactive compounds, including alkaloids, flavonoids, saponins, terpenoids, and tirterpenoids (Budikania et al., 2021), but it has been reported that alkaloid compounds of BSF extract has the optimal activity including 2-(2-cyclohexylethyl)-N,N-bis(3-methylbutyl)-3-(3-piperidin-1-ylpropyl)benzimidazole-5-carboxamide, Isoxazolo[5, 4-D]pyrimidin-4-amine, 1-Naphthyl carbamate, Butoctamide, N-(2-Hydroxyethyl)dodecanamide, Verpacamide A, N-ethenylaniline, N-tert-butyl-N-[[4-[2-[(ditert-butylamino)methyl]pyridin-4-yl]pyridin-2-yl]methyl]-2-methylpropan-2-amine, ethane; (3Z,6Z)-5-imino-N,N,3-trimethyl-8-[5-[(4-

methyl-1-bicyclo[4. 1.1]octanyl)methyl]-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrol-1-yl]nona-1,3,6,8-tetraen-4-amine (Sulistiyani et al., 2023). Alkaloids are a group of compounds known to have various pharmacological activities, including as antibacterials (Maisarah et al., 2023). This causes BSF larvae potentially can be developed as antibacterial agents. However, research on their effectiveness against Gram-positive bacteria is still limited.

One of the most commonly found Gram-positive bacteria as an infectious agent is *Staphylococcus aureus*. *Staphylococcus aureus* is often found on human skin and known as an opportunistic pathogen that can cause serious infections (Kurniawan et al., 2021). *Staphylococcus aureus* produce various virulence factors, including coagulase enzymes and toxins that contribute to its ability to cause disease. Infections caused by *Staphylococcus aureus* can vary from mild skin infections such as acne to more serious conditions such as sepsis (Taylor & Unakal, 2023). In the case of acne, these bacteria can trigger inflammation and pus formation (Imasari & Emasari, 2021) so they must be treated properly.

The potential of BSF larvae as antimicrobials can be used as an alternative to inhibit *Staphylococcus aureus* in acne. However, there is lack of research that related to the inhibition of *Staphylococcus aureus* from acne isolates by BSF larvae, so it is necessary to conduct research to determine the effectiveness of its inhibition against *Staphylococcus aureus* acne isolates. In the end, information related to antibacterial activity can be the basis for the development of topical preparations from BSF larvae. This requires a review of pharmacokinetic aspects, especially skin permeability. Skin permeability is an important factor in the effectiveness of topical preparations because it determines the extent to which active compounds can penetrate the skin layer and reach their therapeutic targets (Christinne & Amalia, 2023). In addition, evaluation of the potential for irritation or allergic reactions is also important to ensure the safety of use in silico. Therefore, this study aims to evaluate the potential of BSF larvae aqueous fraction extract as an antibacterial agent against acne-causing *Staphylococcus aureus* as well as predict skin permeability characteristics and possible irritation effects in In silico.

METHOD

Tools and Materials: Tools used in this study include maceration extraction jars, Rotary evaporator (IKA RV10 Digital V), waterbath (Memmert), UV-Vis spectrophotometer, incubator (Memmert), autoclave (American 75X), analytical balance (Ohaus PX224), micropipette (Dragon Med), measuring cup (Iwaki Pyrex), beaker (Iwaki Pyrex), stirring rod (Iwaki Pyrex), test tube (Iwaki Pyrex), test tube rack, porcelain cup, petri dish, bunsen burner, calipers, tweezers, and sterile cotton. The materials used in this study were BSF larvae (Hermetia illucens), culture of *Staphylococcus aureus* bacterial acne isolate, 96% ethanol (96% ethyl alcohol), distilled water, n-hexane (Gettysolve-B), Ethyl acetate (acetoxyethane), Nutrient Agar (NA), Mueller-Hinton Agar (MHA), Mannitol Salt Agar (MSA), ciprofloxacin antibiotic, sterile blank discs (Himedia), Turbidity Standard Solution 0.5 Mc. Farland I Turbidity Standard Solution (108 CFU/ml), 0.9% Sodium Chloride (NaCl 0.9%), Hydrogen Peroxide (H_2O_2), and Blood Agar Plate (BAP) media.

Extraction and Fractionation: Maceration was carried out in a ratio of 1:10 (b/v) using 96% ethanol for 5 days with stirring at least once a day (Hikmawanti et al., 2023). The macerate was evaporated using a rotary evaporator at 60ºC and then concentrated with a waterbath at 60ºC to form a thick extract of BSF larvae (ELBSF) (Muthmainnah, 2017). ELBSF was fractionated using n-hexane, ethyl acetate, and distilled water. A total of 10 grams of ELBF dissolved in 100 mL of distilled water was put into a separatory funnel along with 100 mL of each solvent variation (1:1). The separatory funnel was shaken and left until two separate

layers were formed. The fractionated ELBSF was then evaporated using a water bath at 60°C to obtain a thick extract that had been fractionated (Susmayanti & Rahmadani, 2023). The yield is expressed as a percentage of weight per weight (%b/b) (Afifah et al., 2023). The extract used for further analysis is the water fraction (FABSF).

Secondary Metabolite Screening: Secondary metabolite screening was conducted to determine flavonoid, polyphenol, alkaloid, saponin compounds in FABSF. Flavonoid testing with Wilstater Cyanidin method is by using magnesium powder (Mg) and concentrated hydrochloric acid (HCl). If the solution contains flavonoid compounds it will show a red or yellow colour. Testing for polyphenol compounds is done using FeCl3. If the solution contains polyphenol compounds it will show blue to dark blue or blackish green colour. Alkaloid compounds are carried out using dragendrof, Mayer, and Wagner reagents. The reaction with dragendrof will form an orange precipitate, the reaction with Mayer will form a white precipitate, the reaction with Wagner will form a reddish brown precipitate. Testing of terpenoid compounds used Liberman Burchard Reagent. If the solution contains terpenoid compounds it will result in blue to dark blue or blackish green colour. Testing for saponins by shaking vigorously for 1 minute, then adding 2 drops of 1 N HCl. If the solution contains saponins, stable foam will form (Muthmainnah, 2017; Budikania et al., 2021; Syafitri et al., 2023).

Antibacterial Activity Test

1. Disc Method
   Staphylococcus aureus was isolated from acne after obtaining an ethically acceptable letter number 96/EC/KEPK/VI/2024. *Staphylococcus aureus* was identified through gram painting, BAP media, catalase test, coagulase test, MSA, and pigmentation observation. *Staphylococcus aureus* that will be tested has a purple cocci colour, BAP positive β hemolysis, MSA positive mannitol fermentation, yellow pigment, positive catalase, and positive coagulase (Sari et al., 2024), then suspended for comparing with Mac Farland 0.5. For antibacterial activity test, bacteria were inoculated on MHA plate media with the spread plate method, then each blank disc was impregnated with 50 µl of extract according to the predetermined FABSF concentration. The FABSF concentration variations used were 40%, 80%, and 100%. FABSF-impregnated discs were then placed on MHA media that had been inoculated with bacteria and incubated for 24 hours at 37°C. After incubation, the zone of inhibition was measured and reported in mm (Sayekti et al., 2023).

2. Determination of Percentage of Microbial Decline
   Determination of the percentage of microbial decline was carried out using a UV-Vis Spectrophotometer. *Staphylococcus aureus* suspension that has been equivalent to Mc Farland 0.5 was taken as much as 50 µL and then put into each sterile test tube containing 950 µL BHI-B media. FABSF with a concentration of 40%, 80%, and 100% as much as 500 µL was added. Ciprofloxacin was used as positive and distilled water as negative control. The mixture of 950 µL BHI-B, 50 µL NaCL, and 500 µL test solution was used as blank control. The results were observed by measuring the absorbance at a wavelength of 600 nm. The percentage of microbial reduction was calculated using the following formula:

$$\frac{Abs\ KN - Abs\ FABSF}{Abs\ KN}\ x\ 100\%$$

   Description:
   Abs KN: Absorbance value of Negative Control.
   Abs FABSF: Absorbance Value of Positive Control FABSF

In Silico Test: Acer Nitro 5 Laptop with specifications of 16.0 GB RAM, 12th Gen Intel(R) Core(TM) i5-12500H 3.10 GHz, Microsoft Windows 11 Home Single Language operating system, and internet connection were used as tools in this in silico test. The active compounds of BSF larvae (*Hermetia illucens*) obtained from PubChem were downloaded through PubChem (http://www.ncbi.nlm.nih.gov/). SMILES Online Translator, Colonical SMILES active compounds were retrieved on the web (https://cactus.nci.nih.gov/translate/). Furthermore, the data was entered into the "Provide SMILES a Strings" column in ADMETlab 3.0 (https://admetlab3.scbdd.com/). The results obtained were then analysed descriptively to evaluate the permeability characteristics of the skin as well as the likelihood of irritation . Obtaining an ethically acceptable letter number 96/EC/KEPK/VI/2024

RESULT

Extraction and Secondary Metabolite Screening

Table 1.
Yield ELBSF and FABSF

Yield of 500 Grams BSF Larvae	
Sample	Yield
ELBSF	15,95%
Yield of 40 Grams ELBSF	
Sample	Yield
FABSF	37,75%

Table 1 showed that ELBSF yield of 15.95% was obtained from 500 grams of BSF larvae. FABSF with a yield of 37.75% was obtained from 40 grams of ELBSF. These results showed that the yields of ELBSF and FABSF are more than 10%.

Table 2.
Secondary Metabolite Yield

Active Compound		FABSF Result
Flavonoid		Positive
Polifenol		Negative
Alkaloid	Dragendrof	Positive
	Wagner	Positive
	Mayer	Negative
Terpenoid		Negative
Saponin		Positive

Table 2 shows that FABSF contains flavonoids, alkaloids (Dragendorff and Wagner), and saponins, but does not contain polyphenols, terpenoids, and alkaloids based on the Mayer test.

Antibacterial Activity Results

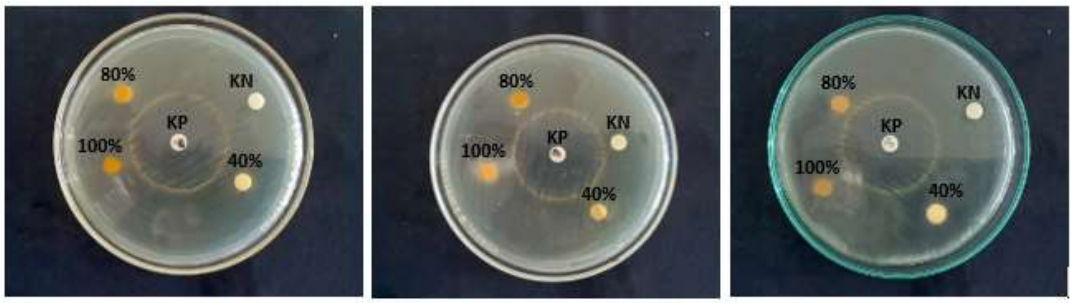
Table 3.
Identification Results of *Stapylococcus aureus* Bacteria

Test	Results
Gram stain	Purple cocci
BAP media	Positive Haemolysis β
MSA	Fermenting mannitol
NA Pigmentation	Tilted Yellow
Catalase	Positive
Coagulase	Positive

Table 3. The identification results of the acne isolate showed that the characteristics of the tested bacteria were in accordance with *Staphylococcus aureus*, namely Gram-positive bacteria in the form of cocci, able to perform β haemolysis on BAP media, and can ferment

mannitol on MSA media. In addition, these bacteria produce yellow pigments on NA slant agar and show positive results in the catalase and coagulase tests.

1. Disc Method



A B C

Table 4.
Antibacterial Activity

Replications	Zone of Inhibition (mm)				
	Negative Control	Concentration			Antibiotics Ciprofloxacin
		40%	80%	100%	
I	0	0	0	0	29,43
II	0	0	0	0	29,45
III	0	0	0	0	29,10
Mean ±SD	0±0	0±0	0±0	0±0	29,32±0,19

Table 4. The inhibition zone results of 0±0 mm showed that FABSF samples at various concentrations did not form an inhibition zone against *Staphylococcus aureus*. The antibiotic ciprofloxacin showed an inhibition zone with an average diameter of 29.32 ± 0.19 mm.

2. Determination of Percentage of Microbial Decline

Table 5.
Percentage of Microbial Decline

Groups	Absorbance			Mean	±SD	Microbial Decline (%)
	I	II	III			
Negative Control	0,9073	0,8971	0,8872	0,8972	±0,0100	0%
Positive Control	0,0385	0,0378	0,0408	0,0390	±0,0015	95,65%
FABSF 40%	0,1162	0,1101	0,1648	0,1303	±0,0299	85,47%
FABSF 80%	0,1078	0,1366	0,1084	0,1176	±0,0164	86,89%
FABSF 100%	0,0695	0,0667	0,1117	0,0826	±0,0252	90,79%

Table 5. Negative control had an average absorbance of 0,8972 ± 0,0100, with a percentage of microbial reduction of 0%, positive control with an absorbance of 0,0390 ± 0,0015 and a percentage of microbial reduction of 95,65%. FABSF 40% showed a microbial reduction of 85,47% with absorbance of 0,1303 ± 0,0299, while at 80% the microbial reduction reached 86.89% with absorbance of 0,1176 ± 0,0164. FABSF 100% showed the highest effectiveness among the concentrations with an absorbance of 0,0826 ± 0,0252 and a microbial reduction of 90.79%.

In Silico Test Results

Table 6.
Skin Permeability Results

No.	Compound	Skin Permeability			Potential Allergy or Skin Irritation	
		TPSA	logP	logS	Skin Sensitization	Skin Sensitisation Rule
1	N-ethenylaniline	12.03	1.884	-1.454	0.913	2 Tanda
2	Isoxazolo[5,4-D]pyrimidin-4-amine	77.83	0.25	-1.992	0.324	2 Tanda
3	1-Naphthyl carbamate	52.32	2.01	-2.956	0.363	1 Tanda
4	Butoctamide	49.33	2.374	-2.394	0.863	0 Tanda
5	N-(2-Hydroxyethyl) dodecanamide	49.33	2.971	-3.702	0.993	0 Tanda
6	Verpacamide A	113.81	-0.626	-1.313	0.876	1 Tanda
7	N-tert-butyl-N-[[4-[2-[(ditert-butylamino)methyl]pyridin-4-yl]pyridin-2-yl]methyl]-2-methylpropan-2-amine	32.26	6.056	-4.82	0.177	0 Tanda
8	ethane;(3Z,6Z)-5-imino-N,N,3-trimethyl-8-[5-[(4-methyl-1-bicyclo[4.1.1]octanyl)methyl]-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrol-1-yl]nona-1,3,6,8-tetraen-4-amine	33.57	3.861	-3.584	0.984	0 Tanda
9	2-(2-cyclohexylethyl)-N,N-bis(3-methylbutyl)-3-(3-piperidin-1-ylpropyl)benzimidazole-5-carboxamide	41.37	7.613	-5.278	0.757	1 Tanda

Description:
- TPSA = Topological Polar Surface Area: Optimal 0-140
- logP = The logarithm of the n-octanol/water distribution coefficient at pH : 7.4
- logS = The logarithm of aqueous solubility value
- Skin Sensitisation = Category 1: Sensitizer; Category 0: Non-sensitizer; Output value is the probability of being toxic, in the range 0 to 1.
- Skin Sensitization Rule = 155 skin irritation substructures

Based on Table 6 Compounds Butoctamide (No. 4), N-(2-Hydroxyethyl) dodecanamide (No. 5), and ethane; (3Z,6Z)-5-imino-N,N,3-trimethyl-8-[5-[(4-methyl-1-bicyclo[4. 1.1]octanyl)methyl]-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrol-1-yl]nona-1,3,6,8-tetraen-4-amine (No. 8) is a good candidate because it has optimal penetration ability and does not cause irritation to the skin. In contrast, Verpacamide A (No. 6) has a TPSA of 113.81 Å², which indicates low skin permeability, making it likely to be difficult to penetrate the epidermis. Compound 2-(2-cyclohexylethyl)-N,N-bis(3-methylbutyl)-3-(3-piperidin-1-ylpropyl)benzimidazole-5-carboxamide (No. 9) has a logP above 5, which indicates it is too lipophilic that it can get trapped in the lipid layer of the skin, hindering optimal penetration. In addition, N-ethenylaniline (No. 1) and Isoxazolo[5,4-D]pyrimidin-4-amine (No. 2) had two skin sensitivity marks, indicating high potential for irritation and allergy, making them less safe for topical use.

DISCUSSION

Extraction of BSF larvae was done using maceration method with 96% ethanol and resulted in an ELBSF yield of 15,95%. During the maceration process, the macerate was stored in a place protected from light to prevent reactions triggered by light or discolouration (Wendersteyt et al., 2021). The advantages of maceration method can maintain the stability of active compounds because the extraction process avoids thermal degradation that often occurs in

heating-based extraction methods (Asworo & Widwiastuti, 2023). Ethanol was used because it is universal and easy to obtain. Ethanol with a concentration of 96% was chosen because it is more selective, non-toxic, has good absorption, and high extraction efficiency. This solvent is able to extract compounds with various levels of polarity, including non-polar, semi-polar, and polar (Wicaksono et al., 2023). In addition, 96% ethanol more easily penetrates the cell wall of the sample compared to lower concentrations of ethanol, resulting in a more concentrated extract (Chandra et al., 2023).

Fractionation is a technique of separating chemical compounds in extracts based on their polarity. This process is carried out to separate compounds according to their polarity using two solvents that do not mix each other and have different levels of polarity. In multistage fractionation, various solvents with different solubilities are used sequentially, thus allowing optimal extraction of secondary metabolite compounds according to their solubility in each solvent (Putri et al., 2023). Fractination of ELBSF obtained 37,75% FABSF which meet the minimum standard of 10% as a good yield value limit (Rahadyana et al., 2024). These results indicate that the process has run efficiently, signalling that the processing and extraction methods have been carried out optimally.

Secondary metabolite screening to identify the active compound content of FABSF showed that FABSF was positive for alkaloids in the Dragendorff and Wagner tests, but negative in the Mayer test, positive for flavonoids, and positive for saponins, while polyphenols and terpenoids were not detected. The presence of alkaloids in FABSF is important in pharmacological potential. Alkaloid, flavonoid, and saponin compounds have potential as antibacterials. Alkaloid compounds can interact with bacterial DNA or proteins so as to inhibit bacterial growth, flavonoid compounds in the extract indicate the potential for strong bioactivity in the mechanism of disruption of the cell wall or enzymatic system of bacteria and saponins show natural detergent properties that can damage bacterial cell membranes (Tridesianti et al., 2025; Sambou, 2024).

The results of the antibacterial activity test using the disc method showed that FABSF at various concentrations of 40%, 80%, and 100% did not form an inhibition zone against *Stapylococcus aureus*, but in comparison, the antibiotic ciprofloxacin showed a significant inhibition zone with an average diameter of 29,32 ± 0,19 mm. This result contradicts the determination of the percentage of microbial decline which showed a value of up to 90,79% reduction. This indicates that FABSF has activity against bacteria, but cannot be measured using the disc method. Factors that cause FABSF to diffuse into the agar medium in the disc method can be influenced by the limitations of the method itself. The disc diffusion method has disadvantages, such as the low osmolarity level of the test solution and the relatively small concentration of extracts used (Rahman et al., 2022). In addition, several other factors also play a role, such as the level of sensitivity of the test organism, the diffusion speed of the antibacterial compound where FABSF has a slower diffusion speed in the agar medium, and the influence of pH. Differences in pH in the media can affect the amount of test substance that diffuses (Hanifa et al., 2022). Testing the disc method of the test sample must diffuse well in the agar medium so that it can inhibit the tested bacteria (Balouiri et al., 2016). The percentage decrease in the number of microbes by FABSF was determined by measuring the absorbance value using a UV-Vis Spectrophotometer. The absorbance measurement results show that FABSF has antibacterial activity against Stapylococcus aureus in liquid media conditions because FABSF concentrations of 40%, 80%, and 100% caused a decrease in the number of microbes by 85,47%, 86,89%, and 90,79%, respectively.

The potency of FABSF in reducing the number of microbes indicates that BSF can be used as an antibacterial agent and developed into topical preparations. Some of the main parameters analysed include Topological Polar Surface Area (TPSA), logP, logS, and skin irritation potential (Skin Sensitization Rule). TPSA is an indicator of a compound's polarity that affects its ability to penetrate biological membranes, including the skin, where values ≤ 140 Å² are considered ideal for skin penetration. LogP indicates the lipophilicity of the compound; values in the range 1-4 are ideal for penetrating the skin without getting trapped in the lipid layer or being too hydrophilic. LogS measures the solubility of the compound in water, which affects the formulation and the efficiency of delivery of the compound through the skin. Meanwhile, the Skin Sensitisation Rule assesses the likelihood of the compound causing irritation or an allergic reaction, with more signs indicating a higher risk of irritation. Based on the results of the analysis, it shows characteristics that are suitable for topical preparation formulations. Butoctamide compound has TPSA 49.33 Å², logP 2.374, and logS -2.394, which indicates good penetration ability as well as sufficient solubility for formulation, with very low risk of irritation as it has no sign of irritation. The compound N-(2-Hydroxyethyl) dodecanamide has the same TPSA, with logP 2.971 and logS -3.702, which is still within optimal limits for skin penetration without risk of irritation. A potential compound is the ethane compound; (3Z,6Z)-5-imino-N,N,3-trimethyl-8-[5-[(4-methyl-1-bicyclo[4.1.1]octanyl)methyl]-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrol-1-yl]nona-1,3,6,8-tetraen-4-amine with a TPSA of 33. 57 Å², logP 3.861, and logS -3.584, which have high permeability and show no irritation potential. These three compounds represent good potential for topical preparations such as creams, gels, or ointments, as they have a balance between solubility, penetration ability, and safety on the skin.

CONCLUSION

FABSF has the potential to be developed as an antibacterial agent and topical preparation because it can reduce *Staphylococcus aureus* by up to 90.79% and in silico is suitable for topical preparations. In Silico tests through skin permeability analysis and irritation potential showed that Butoctamide, N-(2-Hydroxyethyl) dodecanamide, and ethane;(3Z,6Z)-5-imino-N,N,3-trimethyl-8-[5-[(4-methyl-1-bicyclo[4.1.1]octanyl)methyl]-2,3,3a,4,6,6a-hexahydropyrrolo [2,3-c]pyrrol-1-yl]nona-1,3,6,8-tetraen-4-amine compounds are suitable for topical preparations.

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