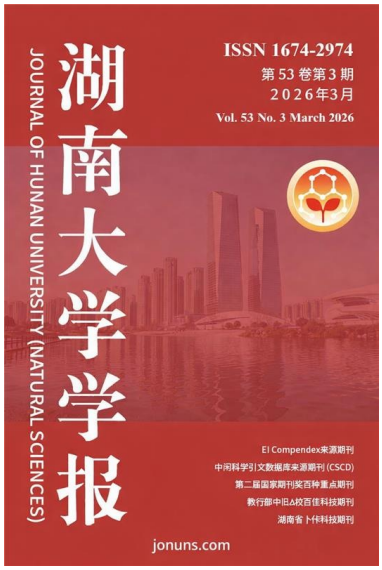

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Multi-Approach Assessment of *Albizia saponaria* Bioactivity Against Dandruff-Related Bacteria and Fungi

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Abstract: Dandruff and fungal-associated alopecia result from microbial dysbiosis, including *Malassezia furfur*, *M. globosa*, *Trichophyton rubrum*, and *Staphylococcus epidermidis*, highlighting the need for alternative therapeutics with improved safety. This study evaluates the antimicrobial activity of *Albizia saponaria* stem bark against dandruff-associated microorganisms and identifies the key bioactive metabolites responsible. The work combines in vitro bioassays and GC-MS profiling. Pharmacokinetic screening and molecular docking provide

mechanistic insights. Ethanolic extracts were fractionated using hexane, ethyl acetate, butanol, and water, followed by antimicrobial evaluation. The hexane fraction showed the most potent antifungal activity, with inhibition zones of 18.25±1.53 mm (*M. furfur*), 21.64±1.80 mm (*M. globosa*), and 22.00±2.35 mm (*T. rubrum*), significantly higher than other fractions ($p<0.05$). Its activity against *T. rubrum* was comparable to ketoconazole ($p>0.05$). GC-MS identified 21 predominantly lipophilic metabolites, including fatty acid esters, terpenoids, phenolics, and sterol derivatives. Docking analysis revealed notable binding affinities, ranging from -4.3 to -9.5 kcal/mol, with 4-campestene-3-one and norambreinolide exhibiting interactions comparable to ketoconazole at CYP51 and TcaR. Collectively, the results demonstrate that the hexane fraction contains multiple bioactive metabolites with strong antimicrobial potency, mechanistic relevance to ergosterol disruption, biofilm inhibition, and metabolic interference. These findings highlight the hexane fraction as a credible natural antidandruff candidate, warranting further isolation studies and in vivo evaluation.

Keywords: Albizia saponaria; Antimicrobial; GC-MS; Molecular docking.

Albizia saponaria 对头皮屑相关细菌和真菌的生物活性多方法评价

摘要： 头皮屑及真菌相关性脱发源于微生物群失衡，包括*Malassezia furfur*、*M. globosa*、*Trichophyton rubrum* 和 *Staphylococcus epidermidis*，凸显了开发安全性更高的替代疗法的必要性。本研究评估了皂荚合欢（*Albizia saponaria*）干树皮对头皮屑相关微生物的抗菌活性，并鉴定其主要生物活性代谢物。研究结合了体外生物测定和 GC-MS 分析，并通过药代动力学筛选和分子对接提供机制性见解。采用乙醇提取物，并通过正己烷、乙酸乙酯、丁醇和水进行分级分离，随后进行抗菌活性评估。正己烷分级展现出最强的抗真菌活性，其抑菌圈分别为 18.25±1.53 mm（*M. furfur*）、21.64±1.80 mm（*M. globosa*）和 22.00±2.35 mm（*T. rubrum*），显著高于其他分级（$p<0.05$），且对 *T. rubrum* 的活性与酮康唑相当（$p>0.05$）。GC-MS 鉴定了 21 种主要疏水性代谢物，包括脂肪酸酯、萜类化合物、酚类及甾醇衍生物。分子对接分析显示其结合亲和力显著，范围为 -4.3 至 -9.5 kcal/mol，其中 4-坎培斯-3-酮及诺安布雷内内酯与酮康唑在 CYP51 和 TcaR 的作用相当。综合结果表明，正己烷分级含有多种生物活性代谢物，具有显著抗微生物活性，并通过干扰麦角甾醇合成、抑制生物膜及代谢干扰发挥作用。这些发现突出了正己烷分级作为天然抗头皮屑候选物的潜力，支持进一步的分离研究及体内验证。

关键词：皂荚合欢（*Albizia saponaria*）；抗微生物；GC-MS；分子对接

1. Introduction

Alopecia is a disease characterized by excessive hair loss (more than 100 strands per day), which eventually leads to baldness. Epidemiological data showed that alopecia affects approximately 2% of the world's population [1]. Alopecia can happen when the immune system does not work correctly, chemotherapy or radiation therapy has side effects, drugs have side effects, there are too many androgen hormones, or there are fungal infections. Approximately 65% of patients undergoing chemotherapy experience alopecia [2], escalating to 90% among those receiving radiation therapy [3]. Furthermore, 20.4% of alopecia cases have been linked to dandruff resulting from fungal infections. A study by Khan et al. (2024) reported that 77.3% of people of reproductive age (18-24 years) in Pakistan suffer from fungal infections of the scalp, leading to dandruff. The susceptibility to fungal infections in tropical climates accounts for the high prevalence of alopecia in Indonesia. The peak incidence occurs in young adults around the age of 20 [4]. The fungi responsible for dandruff include *Malassezia furfur*, *M. globosa*, and *Trichophyton rubrum*. These fungi are part of the normal scalp flora but can proliferate under conditions of excessive sebum secretion. In addition, *Candida albicans* and *Staphylococcus epidermidis* are also reported to contribute to dandruff formation [5-7]. Therefore, this study focuses on alopecia caused by *S. epidermidis* and fungal infection.

Scalp fungal infections can be treated with griseofulvin, terbinafine, and itraconazole, as well as shampoos or creams containing anti-fungal agents such as ketoconazole or selenium sulfide. Although effective, ketoconazole may cause erythema and even inflammation of hair follicles, whereas selenium sulfide

can lead to dryness, irritation, edema, and itching of the scalp [8,9]. Moreover, excessive use of antifungal agents may lead to the development of resistance, making infections more difficult to treat [10]. These serious side effects have encouraged the search for more effective but safer alternatives, one of which is the use of natural products, such as langir (*Albizia saponaria* L.).

A. saponaria belongs to the subfamily Mimosoideae, with its primary distribution in Kalimantan, the Sunda Shelf, Maluku, and Sulawesi. Empirically, the Tolaki ethnic group in South Konawe Regency and the Bugis in Bone Regency, South Sulawesi, utilize this plant by soaking the stem bark in water until foam is produced, which is then applied to the scalp as an antidandruff shampoo [11]. Phytochemical analysis has demonstrated that ethanol extracts of *A. saponaria* stem bark comprise alkaloids, flavonoids, tannins, saponins, and phenols [12]. Himaniarwati et al. (2022) reported that ethanol and aqueous extracts are effective in promoting hair growth. The aqueous fraction of *A. saponaria* stem bark was able to inhibit the growth of *M. furfur* (d= 18.67 mm) compared to ketoconazole (d= 16.67 mm). In silico studies targeting the enzyme lanosterol 14-α demethylase demonstrated that five metabolites from *Albizia sp*. exhibited stronger binding affinities compared to ketoconazole, namely tamarixetin 3-rutinoside, quercetin 3-rhamnosyl-galactoside, albiziasaponin A, albiziasaponin C, and albiziasaponin D [13]. Preliminary assays also revealed that the ethyl acetate extract exhibited antioxidant activity, scavenging DPPH radicals ($IC_{50,}$ 35.27±2.85 μg/mL) and ABTS radicals ($IC_{50,}$ 60.04±0.98 μg/mL), with a total phenolic content of 4.50±0.01 mg/g and a flavonoid content of 3.55±0.04 mg/g [14].

A. saponaria was selected due to its ethnomedicinal relevance, reported antimicrobial and dermatological properties, and the lack of comprehensive mechanistic studies concerning dandruff-associated microorganisms. Previous literature and preliminary screening suggest that this plant contains secondary metabolites with potential antimicrobial and anti-inflammatory properties. However, most existing studies are limited to crude extracts, with minimal mechanistic interpretation and limited integration between metabolite profiling and biological effects. To address this gap, the present study integrates antimicrobial bioassays, GC-MS chemical characterization, drug-likeness evaluation, and molecular docking to elucidate the antimicrobial potential and underlying mechanisms.

2. Methods

2.1 Collection of samples

The stem bark of *A. saponaria* was harvested from the tropical forest ecosystem of Bone Regency, South Sulawesi, Indonesia, in July 2023, coinciding with the rainy season. Botanical identification was conducted to confirm the taxonomic status of the species. A voucher specimen has been archived in the herbarium collection of the Department of Biological Pharmacy at Almarisah Madani University to ensure reproducibility and verification in future studies.

2.2 Extraction and fractionation of plant material

The stem bark was cleaned, oven-dried at 40°C for three consecutive days and pulverized into a fine powder using a mechanical grinder (Philips, Netherlands). A total of 3.0 kg of the powdered material was extracted by cold maceration using 96% ethanol. The extraction was conducted in three successive cycles, each with 5.0 L of solvent, for 72 h with occasional stirring to enhance solvent diffusion. All extraction steps were performed under reduced light conditions to minimize photodegradation of phytoconstituents. For fractionation, approximately 100 g of the crude extract was suspended in 1.0 L of distilled water and sequentially partitioned with hexane, ethyl acetate, and butanol through liquid-liquid extraction. The residual aqueous phase was designated as the water fraction. Both extract and fractions were evaporated to dryness under vacuum in a rotary evaporator (Buchi).

2.3 Microorganisms and culture conditions

The bacterial strain *S. epidermidis* (ATCC 12228) was used as the test organism. The culture was initially sub-cultured on Nutrient Agar (NA, Merck, Germany) and incubated at 37°C for 24 h to obtain fresh colonies. The fungal strains *M. furfur* (ATCC 14521), *M. globosa* (ATCC MYA-4889), and *T. rubrum* (ATCC MYA-4438) were used as representative pathogenic fungi. Each strain was cultivated on Potato Dextrose Agar (PDA, Merck, Germany) and incubated at 25°C for 72 h under standard culture conditions.

2.4 Determination of minimum inhibitory concentration (MIC)

The antimicrobial activity was evaluated using the broth microdilution method. Bacterial were cultured in Mueller–Hinton Broth (MHB; Merck, Germany) and standardized to 0.5 McFarland turbidity, corresponding to approximately 1×10^8 CFU/mL. Fungal strains were cultured in Potato Dextrose Broth (PDB, Merck, Germany) under appropriate growth conditions. Serial two-fold dilutions of each test sample (31.25, 62.50, 125.00, and 250.00 μg/mL) were prepared in 96-well microplates. After inoculation, plates were incubated at 37°C for 24 h to promote bacterial growth and at 25°C for 72 h under standard culture conditions to support fungal growth. MIC was defined as the lowest concentration showing no visible turbidity when compared with the negative control.

2.5 Sample preparation

A stock solution was prepared by diluting about 100 mg of extract and fractions in 2 mL of 5% DMSO (20% v/v). For a 2-fold dilution (10%): In a sterile Eppendorf pipette, add 500 µL of 0.9% NaCl and then add 500 µL of the stock solution. For a 4-fold dilution (5%): In a sterile Eppendorf pipette, 250 µL of 0.9% NaCl was added, followed by 750 µL of the stock solution. For a 4-fold dilution (2.5%): In a sterile Eppendorf tube, 125 µL of 0.9% NaCl was added, followed by 875 µL of the stock solution. Sterile paper disks (6 mm diameter) were impregnated with 20 µL of each diluted sample and allowed to dry under sterile conditions. The final amounts of sample loaded per disk were 1.0, 0.5, 0.25, and 0.125 mg, respectively.

2.6 Antimicrobial activity assay

The antimicrobial activity of the extracts and fractions was evaluated using the disk diffusion method on agar. For antibacterial assays, bacterial cultures were adjusted to an optical density of 0.5 at 600 nm, and 100 µL of the suspension was inoculated into pre-warmed MHA. The inoculum was homogenized, poured into sterile Petri dishes, and allowed to solidify at room temperature. For antifungal assays, fungal suspensions were standardized to a 1.0 McFarland standard, and 100 µL was inoculated into pre-warmed PDA. Gentamicin (10 µg/disc) and ketoconazole (30 µg/disc) served as positive controls for bacterial and fungal assays, respectively, while 5% dimethyl sulfoxide (DMSO) was used as the negative control. All inoculated plates were incubated under the appropriate growth conditions: bacterial cultures at 37°C for 24 h and fungal cultures at 25°C for 72 h. The antimicrobial activity was determined by measuring the diameter of the inhibition zones around the disks using a digital caliper (±0.01 mm).

The activity index (AI) of all samples was also evaluated to determine the strength of antimicrobial activity against broad-spectrum microorganisms. The AI was calculated by using the formula given below [15]:

$$\mathrm{AI} = \frac{\text{Diameter of zone inhibition of sample}}{\text{Diameter of zone inhibition of standard}} \quad (1)$$

2.7 GC-MS analysis

Briefly, 10 mg of each extract or fraction was dissolved in 10 mL of methanol and filtered prior to analysis. A 10 µL aliquot was injected into the Agilent 6890 gas chromatograph coupled with an HP 5973 mass selective detector. Separation was performed on a DB-5MS column (5% phenyl methyl siloxane) with an internal diameter of 250 µm and a film thickness of 0.25 µm. The oven temperature was initially maintained at 50°C for 3 min, then increased to 315°C at a rate of 10°C/min and held for 10 min. Helium served as carrier gas at a constant flow rate of 1 mL/min. The injector and ion source temperatures were set to 330 and 250°C, respectively. Mass spectra were recorded in full-scan and selected monitoring modes within a mass range of 50-550 m/z, following a solvent delay of 7 min. The resulting chromatographic peaks were matched against the NIST08 library based on both retention time and spectral similarity for identification of primary and secondary metabolites. Data processing was performed using Agilent ChemStation, AMDIS, and the Agilent Deconvoluted Reporting Software (DRS).

2.8 Receptor preparation

Four protein receptors were utilized in this study, namely 1T2P (sortase), 3KP3 (transcriptional regulator, TcaR), 1I6O (carbonic anhydrase, CA), and 6AYB (CYP51/sterol 14α-demethylase). The three-dimensional (3D) structures of these receptors were downloaded from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) in PDB (*.pdb) format. The receptors were subsequently prepared using Discovery Studio 2016 and AutoDock Tools 1.5.6, during which water molecules, heteroatoms, and redundant chains were removed, partial charges were added, and polar hydrogens were assigned. The prepared receptors were then saved in PDBQT (*.pdbqt) format for molecular docking.

2.9 Ligand preparation

Two-dimensional structures of all test compounds were generated using ChemDraw. These structures were converted into 3D conformations using Chem3D, followed by geometry optimization and energy minimization. The optimized ligands were subsequently converted into PDB format using Discovery Studio 2025 and finally prepared for docking using AutoDock Tools.

2.10 Prediction of pharmacokinetic properties

The physicochemical and pharmacokinetic properties of all test compounds were predicted using the SwissADME software. The suitability of each ligand as a potential drug-like molecule was evaluated according to Lipinski's Rule of Five.

2.11 Validation of molecular docking protocol

Docking validation was performed using PyRx, employing the AutoDock Vina algorithm for each receptor with its native co-crystallized ligand. A grid spacing of 1 Å was applied. Configuration files (*.conf) were generated by defining receptor and ligand file names, grid box dimensions, center coordinates, exhaustiveness, and docking modes. The validation

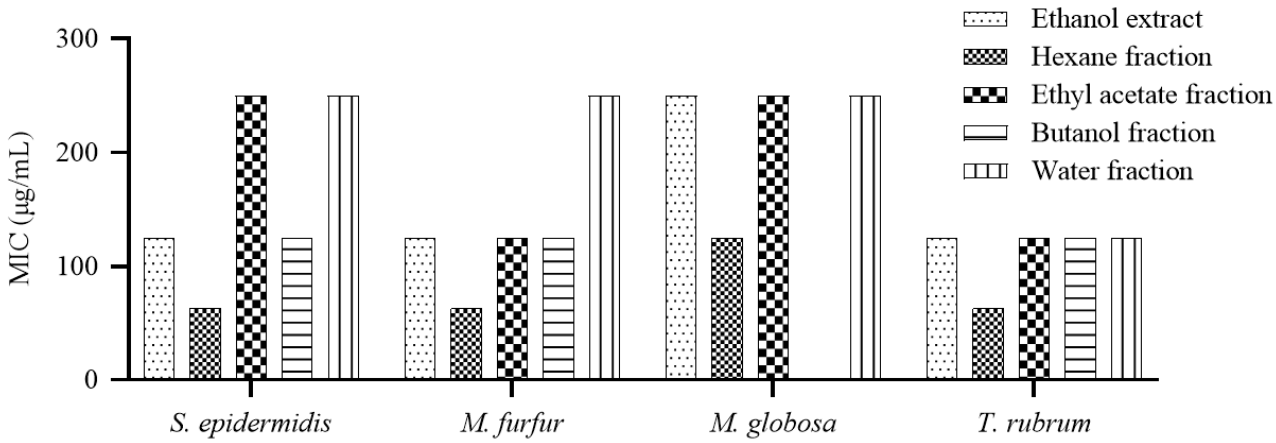

Figure 1. The MIC of *A. saponaria* both in extract and fractions against pathogen microbial. Developed by the authors.

procedure was executed via Command Prompt (cmd) and repeated 20 times to ensure reproducibility. Docking outputs consisted of PDBQT (out) files and TXT (log) files, which were analyzed using LigPlot+ and PyMOL. Validation was considered acceptable when the Root Mean Square Deviation (RMSD) <2.0 Å, indicating the docking protocol successfully reproduced the native ligand pose. Molecular docking was conducted using PyRx with the AutoDock Vina algorithm. Grid box coordinates were determined based on the validated co-crystal ligand binding sites for each receptor. The grid box size used was x= -6.9419, y= -36.335, and z= -17.3629 for 1T2P; x= -6.9419, y= 52.2155, z= 32.8398 for 3KP3; x= 33.9831, y= 0.0000, z =40.5532 for 1I6O; x= 18.6889, y= -0.2599, z= 18.9888 for 6AYB. Docking was performed using the same parameters established during the validation stage.

3. Results

3.1 Value of MIC

The MIC value varied considerably among the crude extract and its solvent fractions, with the hexane fraction consistently exhibiting the most potent inhibition across all tested pathogens, *S. epidermidis*, *M. furfur*, *M. globosa*, and *T. rubrum* (Fig. 1). The ethanol extract and butanol fraction showed moderate and comparable activity against most organisms (125.00 μg/mL), although the butanol fraction displayed an unusually high potency against *M. globosa* with an MIC of 1.00 μg/mL, indicating the presence of a highly active semi-polar compound. In contrast, the ethyl acetate and water fractions were generally less effective, with MIC values predominantly ranging from 125.00 to 250.00 μg/mL. These findings suggest that the principal antimicrobial agents of *A. saponaria* are concentrated in the non-polar hexane fraction, likely terpenoids, fatty acids, and sterols.

3.2 Antibacterial and antifungal activity

The antibacterial and antifungal evaluations of the ethanol extract and its solvent fractions demonstrated marked variation in bioactivity across microbial targets, with the hexane fraction consistently exhibiting the strongest inhibitory performance. Against *S. epidermidis*, the hexane fraction produced the largest inhibition zone among all samples, significantly outperforming the ethanol extract, butanol, ethyl acetate, and aqueous fraction (Fig. 2A). A similar trend was observed in the antifungal assays, where the hexane fraction showed potent inhibition against *M. furfur*, *M. globosa*, and *T. rubrum*, yielding inhibition zones of 18.25±1.53; 21.64±1.80; and 22.00±2.35 mm, respectively (Fig. 2B, 2C, and 2D, respectively). The ethanol extract and butanol fraction display moderate activity across both antibacterial and antifungal assays, with inhibition zones generally ranging from 10 to 16 mm. In contrast, the ethyl acetate and aqueous fractions exhibited the weakest antimicrobial effects, producing zones mostly below 10 mm, indicative of low concentrations of active metabolites. Interestingly, no significant difference was observed between ketoconazole and the hexane fraction against *T. rubrum* ($p>0.05$). The hexane fractions of *A. saponaria* exhibit significant antibacterial and antifungal activity compared with the negative control.

3.3 AI value

The AI evaluation revealed that the hexane fraction exhibited the most potent overall bioactivity against all tested dandruff-associated pathogens, showing the highest index values across *S. epidermidis* (0.67), *M. furfur* (0.70), *M. globosa* (0.86), *and T. rubrum* (1.05),

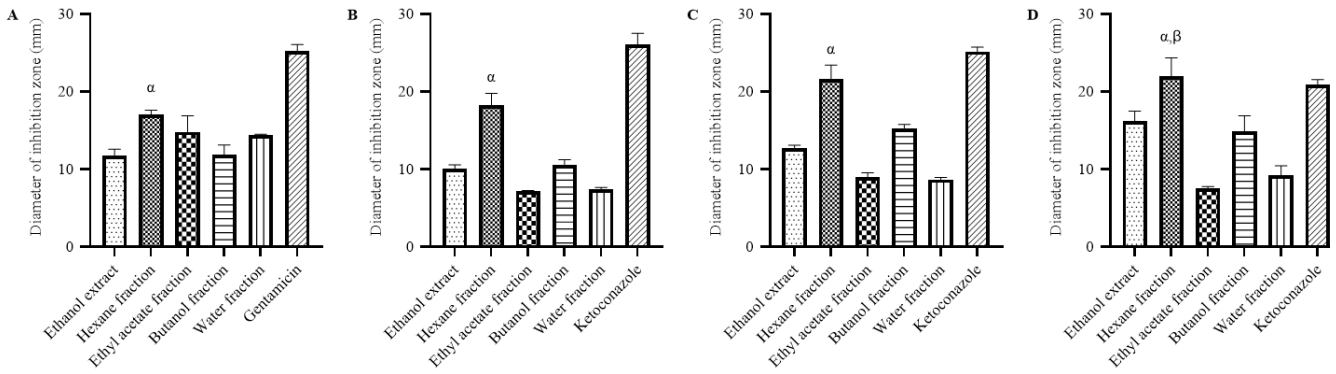

Figure 2. The comparison of antibacterial and anti-fungal activity of *A. saponaria* against (A) *S. epidermidis*; (B) *M. globosa*; (C) *M. furfur*; and (D) *T. rubrum*. Superscribe $^{\alpha}$ is significant to all sample groups; $^{\beta}$ is not significant to ketoconazole. One-way ANOVA followed by Tukey's post-hoc test was conducted, while a p-value <0.05 was considered statistically significant. Developed by the authors.

indicating superior performance relative to other fractions and closely approaching or surpassing the standard drugs depending on the organism (Table 1). The butanol fraction demonstrated moderate activity (0.40-0.71), while the ethanol extract exhibited variable but generally mid-range values (0.38-0.78). In contrast, the ethyl acetate and water fractions showed the lowest activity indices (0.28-0.59 and 0.29-0.57, respectively), suggesting minimal concentrations of bioactive components.

3.4 Metabolite profiles

GC-MS analysis of the hexane fraction revealed a total of 21 identified compounds (Table 2), with retention times ranging from 13.83 to 41.18 min, indicating a chemically diverse composition dominated by hydrophobic secondary metabolites. The chromatographic profile was characterized by the high abundance of 7-tetradecenal (Z) (26.10%), followed by a variety of saturated and unsaturated long-chain molecules, including fatty acids, esters, alcohols, aldehydes, terpenoids, and sterol derivatives. Among these, fatty acids and their esters constituted the largest class, accounting for 12 out of 21 compounds, such as hexadecanoic acid methyl ester, octadecanoic acid, eicosanoic acid ethyl ester, and multiple C18:1 and C18:2 methyl esters. These were accompanied by three long-chain alcohols, including 9-octadecen-1-ol and n-nonadecanol-1, and two aldehydes, with 7-tetradecenal as the dominant representative. The fraction also contained three terpenoid-related compounds, including neophytadiene (0.76%), phytol (0.20%), and a bicyclic furanone derivative (0.38%). Minor constituents included 2,4-di-tert-butylphenol (0.18%) and a sterol derivative, 4-campestene-3-one (0.18%). Overall, these chemical classes collectively demonstrate that the hexane fraction of *A. saponaria* is rich in lipophilic bioactive molecules which can be associated with antimicrobial activities.

3.5 Phytochemical drug-likeness assessment

Table 3 summarizes the drug-likeness evaluation of the 21 metabolites identified in the hexane fraction of *A. saponaria* based on Lipinski's Rule of Five. In general, most compounds have molecular weights below 500 Da, which fulfills one of the key criteria for favorable oral bioavailability and passive membrane permeability. Their hydrogen-bond donor (≤5) and acceptor (≤10) count also fall within acceptable limits, indicating that these molecules have the potential to interact with biological targets without compromising membrane diffusion. Additionally, their molar refractivity values (40-130) fall within the recommended range, suggesting optimal molecular size, polarizability, and compatibility with pharmacokinetic requirements. Most dominant compounds, such as 7-tetradecenal, 7-octadecenoic acid methyl ester, 9,12-octadecadienoic acid methyl ester, phytol, and neophytadiene, match most Lipinski parameters but exhibit relatively high mLogP values, with several exceeding the recommended threshold of 5. Furthermore, minor constituents such as 2,4-di-tert-butylphenol, isopropyl palmitate, and cis-10-heptadecenoic acid also exhibit balanced drug-likeness profiles, characterized by low hydrogen-bonding capacity, moderate molecular refractivity, and suitable physicochemical properties.

3.6 Binding affinities

The molecular docking assessment of 21 metabolites from the hexane fraction revealed a broad range of binding affinities (-4.3 to -9.5 kcal/mol) toward key dandruff-associated targets (Table 3). Sterol-like metabolites such as 4-campestene-3-one exhibited the strongest interaction, particularly with CYP51 (-9.5 kcal/mol), while the bicyclic lactone showed similarly high affinity for TcaR and CA (-9.1 to -9.0 kcal/mol). Long-chain fatty acid esters, including 9,12-octadecadienoic acid methyl ester and eicosanoic acid ethyl ester, demonstrated consistently favorable binding across multiple targets (-7.5 to -8.5 kcal/mol),

Table 1. The AI value of *A. saponaria* both in extract and fractions against pathogen microbial. Developed by the authors.

Sampel	MIC (μg/mL)			
	S. epidermidis	*M. furfur*	*M. globosa*	*T. rubrum*
Ethanol extract	0.47	0.38	0.51	0.78
Hexane fraction	0.67	0.70	0.86	1.05
Ethyl acetate fraction	0.59	0.28	0.36	0.36
Butanol fraction	0.47	0.40	0.61	0.71
Water fraction	0.57	0.29	0.35	0.44
Gentamicin	1.00	0.00	0.00	0.00
Ketoconazole	0.00	1.00	1.00	1.00

suggesting a multifunctional inhibitory profile. Although ketoconazole showed the strongest interactions overall (-9.6 kcal/mol), several metabolites displayed comparable binding behavior, highlighting the hexane fraction as a rich source of lipophilic scaffolds with potential inhibitory activity against fungal ergosterol biosynthesis, biofilm regulation, and CA-mediated metabolism.

4. Discussion

Dandruff is a multifactorial condition driven by the complex interaction between *S. epidermidis*, *M. furfur*, *M. globosa,* and *T. rubrum*, all of which contribute to scalp barrier disruption and inflammation. An overgrowth of *S. epidermidis* contributes to further scalp irritation through the formation of biofilms and the release of inflammatory mediators [5]. Malassezia species dominate the scalp microbiome and initiate dandruff formation through the hydrolysis of sebum, generating pro-inflammatory free fatty acids that alter keratinocyte turnover [6]. *M. furfur* exacerbates the inflammatory cascade by producing oxidative metabolites that intensify erythema and desquamation, while *M. globosa* plays a central role through high lipase activity [7]. Meanwhile, the presence of *T. rubrum* may aggravate symptoms by degrading keratin and weakening the stratum corneum, allowing deeper microbial penetration. Collectively, this dysbiosis amplifies flaking and inflammation, reinforcing the multifactorial nature and persistence of dandruff.

The results of this study demonstrated that the hexane fraction exhibits significant antibacterial and antifungal activity against dandruff-associated organisms, outperforming more polar fractions. The superior inhibition zones produced by the hexane extract indicate that non-polar constituents are the primary contributors to antimicrobial activity. This aligns with previous findings in other *Albizia* species where non-polar fractions consistently exhibit more potent antimicrobial activity due to high concentrations of triterpenoid saponins, sterols, and lipophilic aglycones. Comparable studies by Himaniarwati et al. (2022) showed that the hexane fraction from South Konawe inhibits the growth of *M. furfur* [13]. The antifungal performance parallels patterns seen in related species, such as *A. kalkora*, where hexane fractions exhibited prominent antifungal activity against *Fusarium oxysporum* f. sp. lycopersici [16]. Similar trends have been reported for *A. amara*, in which chloroform extract showed significant antifungal activity, with inhibition zones measured between 11.0±0.0 and 25.6±0.6 mm against *M. globosa* [17]. Notably, the hexane fraction displayed antifungal activity against *T. rubrum* that was statistically comparable to ketoconazole. Similar high-potency effects have been reported for *A. ferruginea* extracts against the fungus *T. rubrum*, with a diameter of zone inhibition of 14 mm [18]. Comparable performance suggests that its non-polar metabolites may contain structurally similar membrane-active compounds capable of inhibiting dermatophyte growth, reinforcing its potential for therapeutic development.

The relatively low antifungal activity of the polar fractions in the present study is consistent with reports across several *Albizia* species, where potent antifungal metabolites are typically concentrated in non-polar fractions. Polar fractions often exhibit weaker antimicrobial activity because most antimicrobial phytochemicals in plants are non-polar or moderately non-polar, allowing them to interact effectively with microbial cell membranes, which are rich in lipids. In contrast, highly polar compounds such as sugars, polysaccharides, tannins, organic acids, and many glycosylated metabolites usually cannot penetrate or disrupt microbial lipid membranes [19]. Antimicrobial mechanisms such as membrane lysis, permeability disruption, and inhibition of sterol pathways require lipophilic compounds that can insert into or destabilize lipid bilayers [20]. The GC-MS analysis further validates the observed biological activity by revealing a metabolite profile dominated by fatty acids, fatty acid esters, long-chain alcohols, terpenoids, phenolics, and sterols. These classes of compounds are widely recognized for their antimicrobial mechanisms, including the disruption of fungal lipid bilayers, increased membrane permeability, inhibition of ergosterol synthesis, and induction of oxidative stress [21]. The abundance of lipophilic metabolites also

Table 2. GC-MS analysis of the metabolite profile of the hexane fraction of *A. saponaria*. Developed by the authors.

Retention Time (Min)	Area (%)	Metabolite name/ligand
13.83	0.22	Gorlic acid
15.57	0.18	2,4-Di-tert-butylphenol
17.10	0.01	Selin-6-en-4 alpha-ol
19.50	0.76	Neophytadiene
19.88	0.14	9-Octadecen-1-ol, (Z)-
21.00	0.41	Hexadecanoic acid, methyl ester
22.39	0.99	Eicosanoic acid, ethyl ester
23.08	0.08	Isopropyl palmitate
23.92	0.13	cis-10-Heptadecenoic acid
24.42	0.27	Octadecanoic acid
24.70	0.10	n-Nonadecanol-1
24.83	0.35	9,12-Octadecadienoic acid, methyl ester
24.98	0.60	7-Octadecenoic acid, methyl ester
25.12	0.09	cis-13-Octadecenoic acid, methyl ester
25.26	0.20	Phytol
26.49	26.10	7-Tetradecenal, (Z)-
30.43	0.22	Butyl 9,12-octadecadienoate
38.73	0.12	Butyl 9-hexadecenoate
39.08	0.18	4-Campestene-3-one
40.40	0.38	Norambreinolide
41.18	0.07	Ethyl 14-methyl-hexadecanoate

explains the vigorous activity against *Malassezia* species, which rely on exogenous lipids for growth. The ability of non-polar metabolites to interfere with lipid assimilation pathways or induce membrane destabilization supports a synergistic mechanism within the non-polar fraction [22]. Fatty acids, terpenoids, aldehydes, and sterol derivatives are characteristic of species within the *Albizia* genus, which are known to accumulate in membranes [16]. The predominance of 7-tetradecenal, unsaturated fatty acids, and terpenoids aligns with reported bioactive constituents in some species, reinforcing the role of hydrophobic phytochemicals in microbial inhibition [23].

Among the compounds identified in the hexane fraction, 2,4-di-tert-butylphenol stands out as a well-documented bioactive agent with broad antimicrobial and antifungal potential. Medeiros et al. (2022) confirmed that 2,4-di-tert-butylphenol has antibacterial, antifungal, and anticancer activities. Experimental studies have shown that 2,4-di-tert-butylphenol can inhibit the growth and virulence factors of *Pseudomonas aeruginosa*, reduce quorum-sensing gene expression, and biofilm formation, suggesting a strong anti-virulence mode of action [24]. Meanwhile, long-chain fatty acids and their methyl or ethyl esters, such as methyl palmitate and C18:2 derivatives (e.g., (9E,12E)-octadeca-9,12-dienoic acid) are increasingly recognized as antifungal agents. Guimarães et al. (2022) reported that unsaturated fatty acids and their derivatives impair fungal growth and mycotoxin production by disrupting cell membranes and interfering with metabolism [21]. The hexane fraction shows superior biological activity compared with other fractions due to its enriched composition of lipophilic bioactive metabolites.

Drug-likeness screening further supports the biological relevance of these metabolites, as most compounds displayed favorable physicochemical properties, a molecular weight of <500 Da, acceptable hydrogen-bond donor/acceptor counts, and optimal molar refractivity, indicating good compatibility with biological membranes. Although many metabolites exhibited high mLogP values, this lipophilic characteristic is advantageous for topical antifungal activity, enabling deeper penetration into the lipid-rich membranes associated with dandruff. Lipophilic compounds, particularly unsaturated fatty acid derivatives, are known to suppress fungal growth by destabilizing membrane bilayers, interfering with lipid metabolism, and inducing oxidative stress [21]. Assessment using Lipinski's Rule of Five confirms these findings, showing that most metabolites fulfill the criteria for molecular weight, hydrogen-bonding capacity, and molar refractivity. However, elevated mLogP, although unfavorable for oral bioavailability, enhances membrane-targeting activity in topical applications [25,26]. Highly lipophilic molecules often interact more effectively with fungal membranes, consistent with reported inhibitory effects against *Malassezia* spp. and *T. rubrum*. Metabolites violating only one Lipinski parameter remain promising candidates, particularly for non-oral delivery routes, where lipid solubility enhances biological performance [26]. The major metabolites identified through GC-MS exhibit favorable pharmacokinetic properties and strong binding affinities to key microbial proteins, consistent with the observed in vitro biological activity.

The docking interactions observed provide mechanistic support for the antimicrobial activity demonstrated by the hexane fraction. These four targets represent interconnected pathways essential for antimicrobial activity. Sortase and TcaR play critical roles in biofilm adhesion, colonization, and virulence, all of which contribute to inflammatory processes on the scalp [27]. CA is responsible for catalyzing the interconversion of carbon dioxide and bicarbonate, a reaction crucial for maintaining pH homeostasis, facilitating cellular respiration, and supporting biosynthetic pathways. Inhibiting CA can impair lipid

Table 3. Drug-likeness screening and binding energy on 1T2P, 3KP3, 1I6O, and 6AYB of the metabolites obtained from the hexane fraction of *A. saponaria.* Developed by the authors.

Ligand	Molecular weight (<500 Daltons)	mlog P (<5)	Hydrogen bond donor (<5)	Hydrogen bond acceptor (<10)	Refractory molar (40-130)	1T2P	3KP3	1I6O	6AYB
1	284.48	5.21	2	2	88.85	-5.1	-7.2	-7.6	-7.9
2	212.37	3.6	1	1	67.94	-5.3	-6.4	-6.9	-7.1
3	224.38	3.83	1	1	70.93	-5.5	-7.9	-7.4	-8.1
4	282.55	7.33	0	0	98.25	-4.8	-6.2	-7.3	-7.7
5	270.49	6.15	1	1	89.8	-4.7	-5.8	-6.5	-6.9
6	272.47	5.51	1	2	86.08	-4.9	-5.7	-6.5	-6.8
7	342.6	7.18	1	2	110.11	-4.7	-7.6	-6.9	-7.8
8	300.52	6.03	1	2	95.69	-5.3	-5.5	-6.6	-7.1
9	272.47	5.27	2	2	86.16	-5.4	-5.8	-7.3	-7.3
10	374.6	5.79	2	4	112.36	-4.8	-6.4	-7.5	-7.4
11	284.52	6.5	1	1	94.61	-5.3	-5.7	-6.7	-7.5
12	286.49	5.58	2	2	90.96	-5.5	-7.8	-7.4	-8.5
13	300.52	6.39	1	1	95.69	-4.8	-7.1	-6.2	-7.4
14	300.52	5.99	1	2	95.69	-4.6	-6	-6.6	-7.3
15	298.55	6.27	1	1	99.42	-5.3	-5.9	-7.2	-7.8
16	214.39	4.67	1	1	70.57	-4.3	-6	-6.2	-6.2
17	342.6	7.13	1	2	110.11	-4.7	-6.2	-6.8	-7.1
18	314.55	6.42	1	2	100.5	-4.9	-5.6	-7.1	-7
19	402.7	6.74	1	1	128.9	-7.8	-7.4	-7.8	-9.5
20	252.39	3.49	1	2	74.45	-6.3	-9.1	-9	-8.4
21	300.52	5.96	1	2	95.69	-4.9	-5.7	-7.1	-7.2
22						-6.3	-6.8		
23								-9.6	-9.6

Note: 21= Gentamicin; 23= Ketoconazole

metabolism and suppress the growth of fungi associated with dandruff [28]. Sterol 14α-demethylase, the primary target of azole antifungal agents such as ketoconazole, is a key enzyme in the ergosterol biosynthetic pathway, which is vital for maintaining fungal cell membrane integrity. Inhibition of this enzyme halts ergosterol production, leading to membrane destabilization and ultimately resulting in fungal cell death [29].

Among all compounds screened, 4-campestene-3-one, a sterol derivative, tetracyclic triterpene, displayed the strongest binding profile (-9.5 kcal/mol), outperforming the control ketoconazole (-9.6 kcal/mol) in one target context. Sterol derivatives, including sitosterol, campesterol, and stigmasterol, exhibit antibacterial and antifungal properties against pathogenic oral microorganisms [30]. Furthermore, norambreinolide exhibited strong activity, with docking values of -9.1 and -9.0 on TcaR and CA, respectively, suggesting potential multi-target inhibition across fungal and bacterial pathways. Norambreinolide exhibited binding energies approaching those of ketoconazole, indicating potential to interfere with pathways such as ergosterol biosynthesis and enzyme-mediated lipid turnover. Long-chain fatty acid esters, including 9,12-octadecadienoic acid methyl ester and eicosanoic acid ethyl ester, also showed strong affinities across multiple targets, supporting previous reports that polyunsaturated fatty acids inhibit fungal enzymes and impair membrane stability [31]. Terpenoids, such as phytol and neophytadiene, further strengthen the extract's activity profile due to their known antifungal, antioxidant, and anti-inflammatory properties [32,33]. For example, a recent patent discloses that topical formulations containing sclareolide inhibited the growth of *M. restricta*, a key yeast implicated in dandruff and seborrheic dermatitis. In the context of scalp physiology, the dual action of sclareolide is particularly relevant because dandruff-prone scalps often exhibit an overgrowth of *Malassezia* species, accompanied by altered bacterial flora and compromised skin barrier integrity [34,35].

5. Conclusion

This study demonstrates that the hexane fraction of

A. saponaria stem bark contains potent antimicrobial compounds capable of inhibiting key microorganisms associated with dandruff, including *S. epidermidis*, *M. furfur*, *M. globosa*, and *T. rubrum*. The potent biological activity correlates with the presence of lipophilic metabolites identified through GC-MS. Lipinski profiling and molecular docking confirm that several compounds possess favorable drug-like properties and exhibit strong interactions with fungal protein targets involved in sterol biosynthesis and membrane regulation. Based on these findings, it is recommended that the hexane fraction of *A. saponaria* be prioritized for further development as a natural antidandruff candidate due to its consistent antimicrobial and mechanistic potential. Future studies should focus on isolating and characterizing individual lead compounds, validating their biological effects through in vivo studies, followed by exploring their safety profiles through cytotoxicity and dermatological assessments. The development of topical formulations, such as shampoos or creams, along with safety and efficacy evaluations, will be crucial to advancing natural alternatives for treating dandruff and fungal-associated alopecia.

Declarations

Author Contributions

Conceptualization, RW, NR, and SF; methodology, LL, NR, and RW; software, LL, and SF; validation, NR, KM, and NR; formal analysis, SF and NR; investigation, LL, NR, SF, and RW; resources, KM and RW; data curation, NR, SF, and RW; writing-original draft preparation, LL, NR, and SF; writing-review and editing, LL, NR, KM, SF, and RW; visualization, LL; supervision, NR and RW; project administration, LL; funding acquisition, RW. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

All data generated or analyzed in this study are fully available within the article.

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Conflicts of Interest

The author declares that there is no conflict of interest regarding the publication of this manuscript.

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