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ORIGINAL ARTICLE / ÖZGÜN MAKALE

INVESTIGATION OF ANTIMICROBIAL, ANTIBIOFILM AND ANTI-QUORUM SENSING ACTIVITIES OF EXTRACTS FROM *SCUTELLARIA YILDIRIMLII* M. ÇİÇEK & A.E. YAPRAK

SCUTELLARİA YILDIRIMLİİ M. ÇİÇEK & A.E. YAPRAK EKSTRELERİNİN ANTİMİKROBİYAL, ANTİBİYOFİLM VE ÇOĞUNLUĞU ALGILAMA İNHİBİSYONU AKTİVİTELERİNİN ARAŞTIRILMASI

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ABSTRACT

Objective: *This study aims to investigate the antimicrobial, antibiofilm, and anti-quorum sensing (anti-QS) properties of extracts derived from the aerial parts of Scutellaria yildirimlii* M. Çiçek & A.E. Yaprak.

Material and Method: *Using a liquid-liquid extraction method, petroleum ether (PEE), ethyl acetate (EAE), and aqueous (AE) sub-extracts were obtained from the total extract (TE) prepared with 80% methanol. Broth microdilution method assessed antimicrobial activity, microplate-based biofilm model and crystal violet assay assessed antibiofilm activity, and disk diffusion method assessed anti-quorum sensing activity*

Result and Discussion: *The extracts exhibited MIC values ranging from 625 to 10000 µg/ml against the tested bacteria. Among them, the TE and PEE extracts showed the strongest antibacterial activity against both Gram-positive and Gram-negative test bacteria. Notably, only the PEE extract demonstrated antifungal activity against Candida albicans ATCC 10231, with an MIC value of 625 µg/ml, while no antifungal activity was observed for the other extracts. However, the antimicrobial effects were generally weak compared to standard antimicrobials. At a concentration of 2500 µg/ml, the biofilm inhibition percentages for AE, TE, PEE, and EAE extracts were 76.79%, 57.47%, 54.81%, and 51.09%, respectively. An anti-QS activity test, conducted based on MIC values against Chromobacterium violaceum ATCC 12472, revealed no violacein inhibition zones, indicating a lack of anti-QS activity. The test results demonstrated that S. yildirimlii possesses greater antimicrobial properties than many other Scutellaria species. This indicates that its extracts could serve as promising candidates for developing treatments against the increasing threat of antibiotic-resistant*

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bacteria. Nonetheless, additional research is essential to thoroughly investigate and confirm the plant's potential as a medicinal resource.
Keywords: *Antibiofilm activity, antimicrobial activity, anti-quorum sensing activity, extraction, Scutellaria yildirimlii*

ÖZ

Amaç: *Bu çalışma kapsamında, Scutellaria yıldırımlii bitkisinin toprak üstü kısımlarından elde edilen ekstrelerin antimikrobiyal, antibiyofilm, ve çoğunluğu algılama mekanizması aktivite potansiyelinin araştırılması amaçlanmıştır.*
Gereç ve Yöntem: *Sıvı- sıvı ekraksiyon metodu ile, %80 metanollü total ektsreden, petrol eteri (PEE), etil asetat (EAE), ve sulu (AE) alt ekstreler elde edilmiştir. Antimikrobiyal aktivite testi, broth mikrodilüsyon metodu ile; antibiyofilm aktivite testi, mikroplaka-bazlı biyofilm modeli ve kristal viyole deneyi ile; çoğunluğu algılama mekanizması aktivite testi, disk difüzyon metodu ile yapılmıştır.*
Sonuç ve Tartışma: *Ekstreler, test edilen bakterilere karşı 625 ile 10.000 µg/ml arasında değişen MIC değerleri sergilemiştir. Bunlar arasında, TE ve PEE ekstreleri, hem Gram-pozitif hem de Gram-negatif test bakterilerine karşı en güçlü antibakteriyel aktiviteyi göstermiştir. Özellikle, PEE ekstreleri yalnızca Candida albicans ATCC 10231'e karşı antifungal aktivite göstermiş olup, MIC değeri 625 µg/ml olarak belirlenmiştir. Diğer ekstrelerde ise herhangi bir antifungal aktivite gözlemlenmemiştir. Ancak, genel olarak, antimikrobiyal etkiler standart antimikrobiyallerle kıyaslandığında zayıf kalmıştır. 2500 µg/ml konsantrasyonda, AE, TE, PEE ve EAE ekstrelerinin biyofilm inhibisyon yüzdeleri sırasıyla %76.79, %57.47, %54.81 ve %51.09 olarak ölçülmüştür. Chromobacterium violaceum ATCC 12472'ye karşı MIC değerlerine dayalı olarak gerçekleştirilen çoğunluğu algılama mekanizması aktivite testi, herhangi bir violasein inhibisyon bölgesi göstermemiştir; bu da çoğunluğu algılama mekanizması aktivitesinin bulunmadığını ortaya koymuştur. Test sonuçları, S. yıldırımlii'nin, birçok Scutellaria türüne kıyasla daha güçlü antimikrobiyal özelliklere sahip olduğunu göstermiştir. Bu durum, bitki ekstrelerinin antibiyotiklere dirençli bakterilere karşı tedavi geliştirme açısından umut verici adaylar olabileceğini düşündürmektedir. Bununla birlikte, bitkinin tıbbi potansiyelinin tam olarak anlaşılması ve doğrulanması için daha fazla araştırma yapılması gerekmektedir.*
Anahtar Kelimeler: *Antibiyofilm aktivite, antimikrobiyal aktivite, çoğunluğu algılama mekanizması aktivitesi, ekstraksiyon, Scutellaria yıldırımlii*

INTRODUCTION

The World Health Organization (WHO) recognizes medicinal plants as a fundamental component of primary healthcare resource for 80% of the global population. Herbal formulations are widely used to address various conditions, such as diabetes, arthritis, liver disorders, and coughs, as well as to enhance memory and function as adaptogens [1]. Since the 1990s, the demand for natural products and innovative applications of medicinal and aromatic plants has grown significantly, driving their increased usage and availability [2].

Scutellaria L. genus (Lamiaceae) is represented by nearly 360-469 species and is known as "skullcap" in the World [3]. Various *Scutellaria* species have been used to treat many diseases, including hepatic and gastric disorders, respiratory, cardiovascular and neurological diseases, cancer, and infectious diseases. The dried root of *Scutellaria* is among the most widely used and versatile medicinal herbs in China and several other Eastern countries. In Turkey, *Scutellaria* has also been utilized, particularly in Anatolian folk medicine, where it is known for its styptic properties, wound-healing effects, and as a general tonic to promote strength. The plant is rich in phytochemicals, including flavonoids, iridoids, neo-clerodanes, and essential oil. Their pharmacological effects, such as anticancer, antioxidative, hepatoprotective, antivirus, anti-inflammatory, and neuroprotective activities have been reported [3,4].

Scutellaria yildirimlii was first identified in the Ayaş region of Türkiye by Mehmet Çiçek and Ahmet Emre Yaprak in 2013. Although it bears botanical similarities to *Scutellaria pectinata* Montbret & Aucher ex Bentham, it differs notably in its dense, woolly hairs. Apart from a few botanical studies [5,6], there has been little to no research on its phytochemical properties or biological activities. In

Turkey, *Scutellaria yildirimlii* taxa has been reported from six different localities in the provinces of Ankara and Eskişehir [5].

The antimicrobial activity of *Scutellaria* species has generally been examined through studies on its essential oil. Studies have shown that essential oil from various *Scutellaria* species, including *S. strigillosa* Hemsley [7], *S. albida* L.subsp. *albida* [8], *S. barbata* D. Don [9], and *S. araxensis* Grosh [10] have been proven to have vigorous antimicrobial activity.

Research has demonstrated the antimicrobial potential of extracts from various *Scutellaria* species. For example, a comparative study on the antimicrobial activities of *Artemisia apiacea* and *S. baicalensis* revealed efficacy against pathogenic fungi and Gram-positive bacteria. Notably, combining the two plants in a 3:5 ratio resulted in enhanced antimicrobial effects [11]. Similarly, an investigation of three *Scutellaria* species native to Türkiye (*S. salvifolia* Benth, *S. diffusa* Benth, and *S. pontica* Karl Koch) reported robust antimicrobial activity [12].

Antibiotic resistance poses a significant global health challenge, leading to infections associated with heightened morbidity and mortality rates. This crisis underscores the urgent need for the development of novel antibacterial therapies. The persistent emergence of resistance to existing antibiotics and the inherent difficulties in discovering new compounds have necessitated the exploration of alternative therapeutic strategies [13,14].

Among these alternatives, quorum sensing (QS) has emerged as a promising target for combating pathogenicity. Quorum sensing plays a pivotal role in regulating virulence factor production and biofilm formation in bacterial pathogens. Recent research has increasingly focused on antibiofilm and anti-QS molecules as potential substitutes for traditional antibiotics. Compounds targeting QS and biofilm formation, particularly those derived from natural sources, are recognized as promising candidates for addressing antibiotic resistance while mitigating the limitations of current antibacterial treatments [15-17].

This study aimed to evaluate the antibacterial, antibiofilm, and anti-quorum sensing properties of extracts obtained from *S. yildirimlii*. The promising results from studies on various *Scutellaria* species, combined with the recent discovery of *Scutellaria yildirimlii* and the lack of research beyond its botanical characterization, have made this species the focus of the present study. This work represents the first investigation into the biological effects of this plant.

MATERIAL AND METHOD

Plant Material

The aerial parts of *S. yildirimlii* M. Çiçek & A.E. Yaprak were gathered on August 7, 2022, from Aşağıkepen village in the Sivrihisar district of Eskişehir province at an altitude of 979 meters. Prof. Dr. Hayri Duman identified the collected plant material, and a voucher specimen (AEF 30989) has been deposited in the Herbarium of the Faculty of Pharmacy at Ankara University.

Preparation of Plant Extract

When the literature is reviewed, it is seen that solvents such as methanol and ethanol, as well as their aqueous mixtures, are frequently used for the extraction of phenolic compounds from *Scutellaria* species [4,9,10]. Based on this, the dried aerial parts of *S. yildirimlii* (200.81 g) were ground and extracted with 80% methanol over a period of 12 days, with each extraction lasting 24 hours. The extract obtained was subsequently filtered and evaporated under vacuum at 40°C, resulting in 27.0977 g of crude extract.

Crude extract (20.0151 g) (TE) was dissolved with 250 ml of distilled water and transferred to a separate funnel. Based on the aqueous methanolic extract, liquid-liquid extraction was performed to obtain sub-extracts with different polarities in order to interpret the active compounds effectively [4,10]. Using petroleum ether and ethyl acetate, liquid-liquid extraction was carried out, as a result, three sub-extracts produces with various polarities: 2.90501 g of petroleum ether extract (PEE), 2.92418 g of ethyl acetate extract (EAE), and 13.0606 g of aqueous extract (AE).

Antimicrobial Activity Assay

The antibacterial and antifungal activities of the extracts were evaluated by using their MIC values with the broth microdilution method [18,19]. For the antibacterial assays, the tested microorganisms included *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 13883, *Pseudomonas aeruginosa* ATCC 27853, and methicillin-resistant *S. aureus* (MRSA) ATCC 43300. The antifungal activity was evaluated using *Candida albicans* ATCC 10231. The plant extracts were prepared in 5% dimethyl sulfoxide (DMSO), and all experiments were performed in triplicate to ensure reliability.

In the antibacterial activity assays, plant extracts were prepared through two-fold serial dilutions in Mueller-Hinton broth, with final concentrations ranging from 10.000 to 78.125 µg/ml. Bacterial inoculums were obtained from 24-hour subcultures and adjusted to a final concentration of 5×10^5 CFU/ml. After the incubation period at 35°C for 18–24 hours, the MIC was determined as the lowest extract concentration that inhibited visible bacterial growth. Negative controls included wells containing only inoculated broth with 5% DMSO, while ampicillin, ciprofloxacin, and gentamicin served as positive controls.

For the antifungal activity assay, plant extracts were prepared in RPMI 1640 broth (ICN-Flow, Aurora, OH, USA; supplemented with glutamine, lacking bicarbonate, and including a pH indicator) using serial two-fold dilutions ranging from 10.000 to 78.125 µg/ml. The fungal inoculum was standardized to a final concentration of $0.5–2.5 \times 10^3$ CFU/ml. Microplates were incubated at 35°C for 48 hours, and the MIC was determined as the lowest concentration that completely inhibited visible fungal growth. Negative controls included wells containing 5% DMSO and RPMI 1640 broth, while fluconazole served as the standard antifungal agent.

Antibiofilm Activity Assay

Before analyzing antibiofilm effects, the MIC of the plant extracts against *Pseudomonas aeruginosa* PAO1 was evaluated. For the antibiofilm evaluation, a sub-MIC concentration of 2500 µg/ml was selected. The testing was conducted using a microplate-based biofilm model and the crystal violet assay [15,20-22].

To biofilm formation, *P. aeruginosa* PAO1 was cultured in Brain Heart Infusion (BHI) Broth for 24 hours at 37°C. Final inoculum suspensions, standardized to approximately 10^6 CFU/ml, were prepared in BHI supplemented with 2% sucrose. A volume of 100 µl of the inoculums was transferred into 96-well microtiter plates in all experimental setups, with incubation at 37°C for 72 hours to achieve fully developed biofilms.

Mature biofilms were first established by removing the medium and washing away non-adherent cells with sterile PBS (pH 7.2). Subsequently, 100 µl of the plant extracts were dispensed into the wells, and the plates were incubated at 37 °C for 24 hours. After incubation, the wells were rinsed with PBS and left to air-dry at room temperature for one hour. To stain the biofilm cells, 100 µl of 0.5% crystal violet solution was added to each well and allowed to incubate for 30 minutes. The wells were then washed three times with PBS, and acetone-alcohol (30:70 v/v) was used to dissolve the bound dye within the biofilm matrix.

BHI broth supplemented with 2% sucrose was served as the control, and the optical density (OD) of the dissolved crystal violet dye was measured at 620 nm using the Microplate Spectrophotometer (Thermo Scientific Multiskan GO/Vantaa, Finland). The percentage of biofilm inhibition was evaluated using the following equation:

$$\% \text{ Biofilm inhibition} = [(OD (\text{Growth control}) - OD (\text{Sample}))/OD (\text{Growth control})] \times 100$$

Anti-Quorum Sensing Activity Assay

Prior to evaluating the anti-quorum sensing (QS) activity, the MIC of the extracts against Chromobacterium violaceum ATCC 12472 was determined. The anti-QS activity was then evaluated using the disc diffusion method, with C. violaceum ATCC 12472 as the reporter bacterium [23,24].

For the assay, the bacterial culture was standardized to a density of 1.5×10^8 CFU/ml. The bacterial suspension was evenly spread onto Luria Bertani (LB) agar plates. Sterile blank discs (6 mm

in diameter; Bioanalyse®, Ankara, Türkiye) were impregnated with 20 µl of the plant extracts and placed on the agar surface. The plates were incubated at 30°C for 24 hours. After incubation, the agar plates were examined for violacein inhibition zones around the discs. The presence of such zones indicated that the plant extracts exhibited anti-QS activity.

RESULT AND DISCUSSION

Antimicrobial Activity Assay

The MIC (minimum inhibitory concentration) values (µg/ml) of *S. yildirimlii* extracts are presented in Table 1. The MIC values against the tested strains varied between 625 and 10000 µg/ml. Among the extracts, the total extract (TE) and petroleum ether (PEE) extracts exhibited the strongest antibacterial activity, effectively inhibiting both Gram-negative and Gram-positive test bacteria. Notably, the PEE extract was the only sample to demonstrate antifungal activity, with a MIC value of 625 µg/ml against *Candida albicans* ATCC 10231, while no antifungal effects were observed for the other extracts. The antimicrobial activities of the extracts were relatively low in comparison to standard antimicrobial agents (Table 1).

Table 1. MIC values (µg/ml) of *S. yildirimlii* extracts

Plant extract	Gram-positive test bacteria		Gram-negative test bacteria			Fungus
	S. aureus ATCC 25923 (MSSA)	*S. aureus* ATCC 43300 (MRSA)	*E. coli* ATCC 25922	*K. pneumoniae* ATCC 13383	*P. aeruginosa* ATCC 27853	*C. albicans* ATCC 10231
Total extract (TE)	625	625	2500	625	5000	-
Petroleum ether extract (PEE)	625	625	625	625	2500	625
Ethyl acetate extract (EAE)	2500	2500	10000	10000	10000	-
Aqueous extract (AE)	1250	1250	10000	1250	10000	-
Ampicillin	1.6	NT	NT	NT	NT	NT
Ciprofloxacin	NT	0.5	<0.25	62.5	<0.25	NT
Gentamicin	NT	<0.25	0.5	NT	<0.25	NT
Fluconazole	NT	NT	NT	NT	NT	1.56
DMSO (%5)	-	-	-	-	-	-

NT: not tested, (-): no activity

Antibiofilm Activity Assay

The biofilm inhibition percentages of *S. yildirimlii* extracts at a concentration of 2500 µg/ml are illustrated in Figure 1. Among the extracts, the aqueous extract (AE) demonstrated the highest antibiofilm activity, achieving a biofilm inhibition rate of 76.79% (Figure 1).

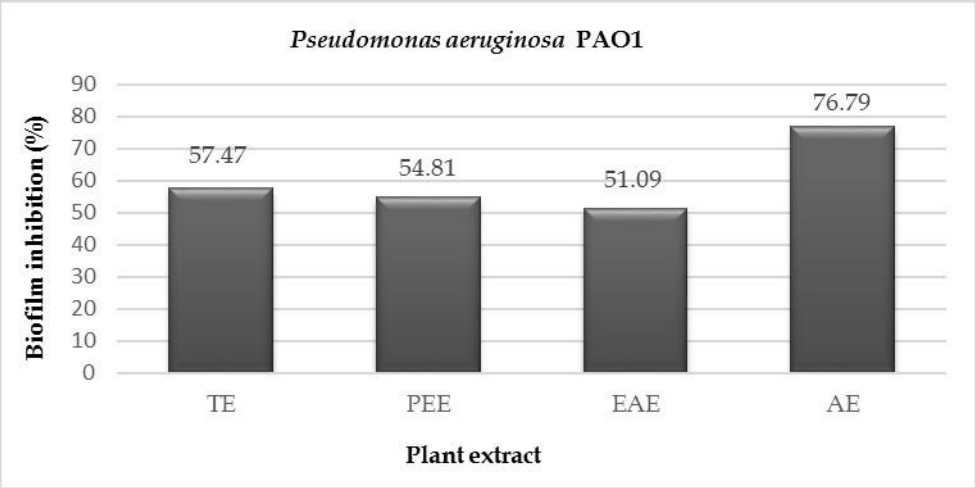

Figure 1. Biofilm inhibition (%) of the *S. yildirimlii* extracts

Anti-Quorum Sensing Activity Assay

The anti-quorum sensing (anti-QS) activity of *S. yildirimlii* extracts was evaluated based on their MIC values against *C. violaceum* ATCC 12472. None of the tested extracts demonstrated violacein inhibition, as no inhibition zones were observed (Figure 2).

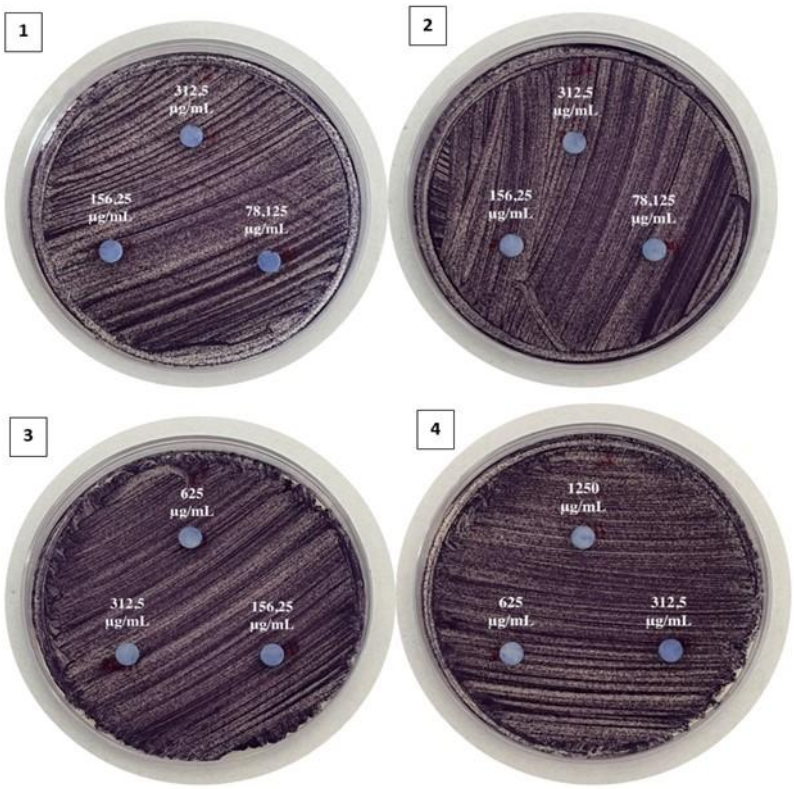

Figure 2. Anti-QS Activity of *S. yildirimlii* extracts (1: TE, 2: PEE, 3: EAE, 4: AE)

Due to the growing threat posed by antibiotic-resistant bacteria to public health, global research efforts on antibiotic resistance have significantly intensified. Studies indicate that bacteria can develop resistance through intrinsic mechanisms or by acquiring resistance to specific antibiotics. The irrational

use of antibiotics exacerbates this problem by preventing antibiotics from reaching their targets, modifying their targets, or inactivating them. These factors contribute to the development and spread of antibiotic resistance [25].

Over the years, various *Scutellaria* species have been reported to exhibit a wide range of pharmacological effects, including anticancer, antibacterial, antimicrobial, anti-inflammatory, antioxidant, antiviral, hepatoprotective, and neuroprotective activities [4]. The selected species within the scope of the study, *S. yildirimlii*, was first described by Mehmet Çiçek and Ahmet Emre Yaprak in Ayaş in 2013 [26]. In a literature study that we conducted, no biological activity and phytochemical studies were found except botanical studies [5,6]. For this reason, the study focuses on evaluating the antimicrobial, antibiofilm, and anti-quorum sensing effects of *S. yildirimlii*.

The antimicrobial activity of *Scutellaria* taxa has generally been studied on their essential oils, including *S. strigillosa* [7], *S. albida* [8], *S. barbata* [9] and *S. araxensis* [10] species, and it has been shown to have strong antimicrobial activity. Although there are few antimicrobial activity studies on extracts obtained from *Scutellaria* species, there are studies on many species, including *S. lateriflora*, *S. baicalensis*, *S. salviifolia*, *S. diffusa*, *S. pontica* and *S. lindbergii*.

S. baicalensis is one of the most studied *Scutellaria* species. A study on this plant revealed that a 70% ethanol extract completely inhibited the growth of *Staphylococcus aureus* at a 10% concentration, *Bacillus subtilis* at a 50% concentration, and *Pseudomonas syringae* at a 50% concentration [27].

In another study conducted with *S. baicalensis*, extracts were prepared using 60, 80 and 100% ethanol and their antimicrobial activity was tested. The results obtained showed a MIC value of 12.5 mg/ml against *S. aureus*, 25 mg/ml against *L. monocytogenes*, and 25 mg/ml against *S. enterica*. Table 1 shows that the least effective extract tested, ethyl acetate, had the same MIC value as the 80% ethanolic *S. baicalensis* extract. Additionally, the most effective extract, petroleum ether, demonstrated significantly stronger activity, with a MIC value of 625 µg/ml [28].

Similarly, the antimicrobial activity test performed on the 70% ethanolic extract prepared from *S. baicalensis* showed a MIC value of 4 mg/ml against *C. albicans*. This value is six times higher than the results of petroleum ether extract obtained from *S. yildirimlii* with MIC value of 625 µg/ml. In contrast, the same experiment revealed that the 70% *S. baicalensis* extract had a MIC value of 0.03125 mg/ml against *S. aureus*, which was considerably lower than the results found in our study [11].

In a study comparable to the present research, 36 extracts were derived from three *Scutellaria* species native to Türkiye (*S. salviifolia*, *S. diffusa*, and *S. pontica*) using various solvents. The antimicrobial activities of these extracts were evaluated against four bacterial strains (*E. faecalis*, *P. aeruginosa*, *E. coli*, and *S. aureus*) and three fungal species (*C. krusei*, *C. parapsilosis* and *C. albicans*). The results indicated that all tested extracts exhibited strong antimicrobial activity against both fungi and bacteria. Among them, the chloroform extract of *S. salviifolia* demonstrated the highest antifungal activity against *C. krusei* (MIC: 32 µg/ml), compared to fluconazole. For antibacterial activity, the chloroform extract from the roots of *S. salviifolia* showed the strongest effect (MIC: 128 µg/ml) against *E. faecalis*, *P. aeruginosa*, and *E. coli*. When compared to the findings of the current study, *S. salviifolia* extracts appear to exhibit higher activity against *S. aureus*, *P. aeruginosa*, and *E. coli* [12].

Another study investigated the antimicrobial activity of methanol, dichloromethane, and ethyl acetate extracts prepared from *S. lindbergii*. The methanol and ethyl acetate extracts (6.25 mg/ml) exhibited the highest activity against *S. aureus*, while the methanol extract (25 mg/ml) was most effective against *E. coli*. The ethyl acetate extract (25 mg/ml) showed the strongest activity against *P. aeruginosa*. All tested extracts had a consistent MIC value (100 mg/ml) against *C. albicans*. The findings of this study indicate that the extracts obtained from *S. yildirimlii* exhibit significantly stronger activity against *P. aeruginosa*, *S. aureus*, *E. coli* and *C. albicans*, with a MIC value of 625 µg/ml [29].

When antibiofilm studies with *Scutellaria* species were examined, a study was found with *S. lateriflora*. In this study, the hydroalkaloid extract derived from the aerial parts of the plant was found to reduce biofilm mass by 68% at a concentration of 55 mg/ml. Furthermore, when combined with 5 mg/ml of *Cistus incanus* at the same concentration, it achieved an 80% reduction in biofilm mass which was slightly higher than the aqueous extract obtained from *S. yildirimlii* (76.79%) [30]. Compared with our study's results, the aqueous extract obtained from *S. yildirimlii* has higher antibiofilm activity than

S. lateriflora alone. No anti-quorum sensing activity test studies conducted with *Scutellaria* species were found.

This study examined the antimicrobial, antibiofilm and anti-QS activities of total (80% methanol), ethyl acetate, petroleum ether and aqueous extracts obtained from the aerial parts of the *S. yildirimlii*. The antimicrobial activity test results revealed that the total and petroleum ether extracts exhibited the most potent antibacterial effects against Gram-positive test bacteria. Additionally, the petroleum ether extract showed the highest antimicrobial activity against both Gram-negative test bacteria and the tested fungus. The antibiofilm activity results indicated that the aqueous extract exhibited the strongest activity, with an inhibition effect of 76.79%. Lastly, no extract tested showed any inhibition of violacein in anti-QS activity results. When these results are compared with literature data, extracts obtained from *S. yildirimlii* have a higher antimicrobial effect than most *Scutellaria* species. This shows that these extracts obtained from *S. yildirimlii* are promising drug candidates against increasingly widespread antibiotic-resistant bacteria. However, more studies certainly needed, to be done with *S. yildirimlii*. The drug potential of the plant should be evaluated further.

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AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this study.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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