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Research Article

Effects of extraction conditions on phenolics content and biological activity of *Equisetum hyemale*

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Abstract: *Equisetum hyemale (E. hyemale)* is a plant rich in bioactive compounds such as alkaloids, flavonoids, phenolic compounds, and silica. These components are known for their potential therapeutic properties, including promoting tissue regeneration and wound healing. This study aims to compare the phenolic compounds content of *E. hyemale* extracts obtained under different extraction conditions and evaluate their effects on antibacterial activity and wound healing. Extraction of *E. hyemale* was performed using different solvents (methanol, ethanol, and water) under varying temperatures and durations in an ultrasonic bath. The obtained extracts were first analyzed by LC-MS/MS to determine the phenolic compound content. Subsequently, the wound healing and antibacterial activities of the extracts were evaluated. The highest phenolic compound content was found in the EH-E-60 and EH-M-60 extracts. The antibacterial activities of the extracts were tested against *S. aureus*, *E. coli*, and PAO1 strains, and the extracts with higher phenolic compound content demonstrated stronger antibacterial activity. The wound healing effects of the plant extracts were also evaluated. Wound width should decrease over time, which is an indicator of healing. In our study, the wound width in the control group was 584.16 µm at the beginning and decreased to 239.64 µm at the end of 72 hours. When EH-E-60 extract was used, the wound width was 593.07 µm at the beginning and decreased to 175.51 µm at 72 hours. These results reveal that the extraction conditions significantly affect the phenolic compounds content and the wound healing process of *E. hyemale* extracts.

INTRODUCTION

In recent years, the use of plants in alternative medicine has significantly increased, primarily due to their phytochemical contents. Compounds such as alkaloids, quinones, phenolic acids, flavonoids, and tannins derived from plants exhibit antimicrobial properties (Cowan, 1999; Mssillou *et al.*, 2022). *E. hyemale*, commonly known as scouring rush, belongs to the Equisetaceae family and contains alkaloids, flavonoids, phenolic compounds, silica, and various other biologically active components (Andrade-Cetto & Heinrich, 2005; Doğan *et al.*,

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2010). *E. hyemale* is widely distributed in tropical and temperate climates and is widespread across nearly all regions of the world (Santos Alves *et al.*, 2019). Typically found along riverbanks, streamsides, marshes, and shallow waters where the stem grows, *E. hyemale* is characterized by fragile, cylindrical, hollow stems reaching approximately 2 meters in height (Gierlinger *et al.*, 2008). Numerous studies have highlighted its effectiveness in treating various ailments, including hypertension, stomach pains, gastric ulcers, rheumatic pains, wounds, burns, cancer, and urinary tract infections (Canales *et al.*, 2005; Li *et al.*, 2022; Santos *et al.*, 2010; World Health Organization, 1998). *E. hyemale* has notable antibacterial, antifungal, antioxidant, and anti-inflammatory properties due to the high levels of phenolic compounds in its structure (de Queiroz *et al.*, 2015; Dos Santos Alves *et al.*, 2016). Phenolic compounds are important secondary metabolites produced by plants, associated with both protective and reproductive functions. These compounds play a crucial role in protecting plants against environmental stresses and defending them against pathogens. Chemically, phenolic compounds consist of one or more hydroxyl (-OH) groups attached to an aromatic hydrocarbon ring. This structural characteristic confers a broad spectrum of biological activities, including antitumor, antioxidant, anti-inflammatory, antiviral, and antimicrobial effects (Abdul Qadir *et al.*, 2017; Chen *et al.*, 2024; Karagöz *et al.*, 2015). Additionally, these compounds are known to support epithelialization (Melguizo-Rodríguez *et al.*, 2021), enhance vasculogenesis and angiogenesis *(Ghodrat et al., 2022)*, increase wound contraction rates (Yin *et al.*, 2015), and regulate inflammatory cytokines (Ambriz-Perez *et al.*, 2016), thereby accelerating the wound healing process.

Various extraction techniques, such as microwave, maceration, and ultrasound using solvents like methanol and ethanol, have been employed to obtain different fractions from *E. hyemale* (Dos Santos Alves *et al.*, 2016; Queiroz *et al.*, 2014; Rodrigues-das-Dores *et al.*, 2020). The yield of these fractions from plant materials is influenced by factors including extraction techniques, solvents, time, temperature, and solvent-to-plant material ratio. Hence, selecting an appropriate extraction method and solvent is crucial for the efficient extraction of targeted bioactive compounds from the plant material (Karabegović *et al.*, 2014).

To date, no studies have investigated the effect of different solvents (water, ethanol, and methanol) on the extraction efficiency of *E. hyemale* fractions or compared the effects of different fractions on wound healing. In this study, for the first time, different fractions of *E. hyemale* were obtained by varying the parameters of ultrasound-assisted extraction, and their chemical compositions were identified using LC/MS to compare their effects on wound healing rates and antibacterial activity.

METHOD

Collection and Identification of *E. hyemale*

E. hyemale was collected from the Kıyakdede region of Şarkikaraağaç district in Isparta. A specimen of the plant (GUL EQ/1/1-1) was identified and deposited in the herbarium of the Department of Biology at Süleyman Demirel University. *E. hyemale* was washed with distilled water to remove foreign particles like dust, and then air-dried at room temperature until completely dry. Dried plant material was ground using a grinder and sieved to obtain particles of a specific size suitable for extraction purposes (Mert Sivri *et al.*, 2023).

Ultrasonication-Assisted Extraction Method

Powdered *E. hyemale* (5 g) was placed in a conical flask, and solvent (methanol, ethanol, or water) was added at a 1:10 ratio (powder to solvent). Then the extraction process was carried out in an ultrasonic bath at different temperatures (25 and 40 ^{o}C), 40 kHz constant frequency, and 0.031 W/mL acoustic power density. The extraction process was also performed at different time intervals (30, 60 min). The parameters changed in obtaining the extract with the ultrasound-assisted extraction method are given in Table 1. The obtained *E. hyemale* extract

was filtered, and the solvent in the extract was removed in a rotary evaporator under vacuum at 40°C. The extract was stored at +4°C until application time.

Table 1. Parameters used in ultrasound-assisted extraction process.

Sample	Sample Code	Solvent	Time (min.)	Temperature (°C)
1	EH-E-30	Ethanol	30	40
2	EH-E-60	Ethanol	60	40
3	EH-M-30	Methanol	30	40
4	EH-M-60	Methanol	60	40
5	EH-W-30-1	Water	30	40
6	EH-W-60-1	Water	60	40
7	EH-W-30-2	Water	30	60
8	EH-W-60-2	Water	60	60

Determination of Components and Their Ratios in the Extracts

LC-MS/MS analysis was performed to determine the components in the *E. hyemale* extract obtained with different solvents and different experimental parameters, and the ratio of these components in the extract. Analyses were performed on a Thermo Scientific TSQ Fortis UHPLC-MS/MS spectrometer equipped with a C18 column (50 × 2.5 mm i.d., 1.9 µm particle size). The mobile phase consisted of 0.1% Formic Acid + 2 mM Ammonium Formate in 95-5% Water-Methanol. The injection volume was 20 µL.

Investigation of Antibacterial Properties of the Extracts

The antibacterial effect of plant extracts prepared under different extraction conditions was investigated on Gram-positive *S. aureus* ATCC 25923 and Gram-negative *E. coli* ATCC 25922 and *P. aeruginosa* PAO1 bacteria using the agar well diffusion method. According to the method, bacterial cultures incubated overnight at 37°C in 5 mL of Luria Bertani (LB) Broth medium were adjusted to a turbidity equivalent to 0.5 McFarland standard at the end of the incubation. 100 µL of these cultures were mixed with 5 mL of LB Agar (0.5% w/v) and poured as a second layer onto pre-poured LB Agar plates. Wells were then created on the solidified agar surface, and 100 µL of plant extracts were loaded into these wells. After loading, the plates were left at room temperature for 30 minutes and then incubated at 37°C for 24 hours. At the end of the incubation, the antibacterial effect was determined by measuring the diameter of the inhibition zones around the wells using a millimetric ruler.

Determination of Minimum Inhibitory Concentration (MIC) Values of the Extracts

The minimum inhibitory concentration (MIC) of the extracts, which were semi-quantitatively determined to have antibacterial effects using the agar well diffusion method, was determined using a method based on microdilution. In this method, 96-well microplates were prepared, and 100 µL of bacterial suspension, adjusted to a turbidity of 0.5 McFarland (108 CFU/mL), was added to the wells containing 100 µL of Mueller Hinton broth with plant extracts, followed by two-fold serial dilutions. The microplates were incubated overnight at 37°C and evaluated after incubation. The lowest concentration at which no bacterial growth was observed was determined as the minimum inhibitory concentration (MIC) value (Andrews, 2001).

Cell Culture Studies of the Extracts

Mouse fibroblast cell line (L929) (ATCC® CCL-1TM) was maintained in Dulbecco's Modified Eagle's Medium (DMEM) with high glucose, supplemented with 10% fetal bovine serum (FBS) and 1% GlutaMAX. The cells were seeded at a density of 5×10^3 cells per well in sterile 96-well plates. *E. hyemale* extract solutions were applied at concentrations of 50, 25, 12.5, and 5 µg/mL, and the cells were incubated for 72 hours. Subsequently, MTT solution was added to each well and incubated for another 3 hours. Absorbance was recorded at 590 nm using the Epoch 2 ELISA plate reader. IC50 values were determined using GraphPad Prism Software 5.

Wound Healing Assay of the Extracts

L929 cells were cultured in a medium containing 90% DMEM, 10% FBS, and 1% GlutaMAX. Cells were plated at a density of 5×10^4 cells per well in 12-well plates and incubated for 24 hours in a humidified environment. After incubation, a scratch was made to create a wound, and the medium was removed. The wells were rinsed multiple times with sterile PBS to remove debris. Fresh medium (1 mL) was added to all wells, with no extracts added to the control wells. Prepared extract solutions (2 µL) were applied to the treatment wells. Wound closure was monitored at 0, 36, and 72 hours, and images were captured using a Leica inverted microscope. Wound widths were analyzed using the ImageJ software.

RESULTS

In this study, the efficacy of extracts from *E. hyemale* in different solvents and temperatures and their effects on wound healing were examined. As can be seen in Table 2, the type of solvent and extraction time have an effect on the extraction efficiency of the plant.

Table 2. Yields of extracts from *E. hyemale* with different solvents and parameters.

Sample	Yield%
EH-E-30	7.76
EH-E-60	12.60
EH-M-30	6.55
EH-M-60	10.44
EH-W-30-1	7.73
EH-W-60-1	11.45
EH-W-30-2	10.16
EH-W-60-2	12.62

LC-MS/MS analysis was used to determine the phenolic compounds of the extracts obtained under different conditions. The analysis results are given in detail in Table 3. According to the results of LC-MS/MS analysis, *E. hyemale* was found to contain high amounts of rutin and quercetin compounds. Additionally, it was determined that the EH-W-30-2 and EH-W-60-2 extracts, obtained under different extraction conditions, contained a high concentration of phenolic compounds.

Table 3. LC-MS/MS results of extracts from *E. hyemale* with different solvents and parameters.

Components (mg/kg)	Samples							
	1	2	3	4	5	6	7	8
Epigallocatechin	0.163	0.176	0.152	0.155	0.142	0.172	0.181	0.177
Epigallocatechin-gallate	0.321	0.348	0.308	0.316	0.276	0.346	0.363	0.355
Epicatechin-gallate	1.663	1.758	1.597	1.637	1.447	1.805	1.846	1.850
Caftaric acid	3.145	3.390	2.956	3.036	2.705	3.324	3.585	3.408
Cyanidin	19.267	20.905	17.726	18.098	17.148	20.770	21.772	21.291
Epicatecin	5.205	5.501	4.840	4.961	4.112	5.647	5.933	5.789
Gallocatechin	0.199	0.215	0.191	0.196	0.169	0.211	0.229	0.216
Caffeic acid	13.330	14.463	12.530	12.793	11.597	14.370	14.663	14.730
Catechin	12.486	13.198	11.487	13.487	10.738	13.548	13.485	11.888
p-coumaric acid	9.753	10.514	9.070	9.315	8.680	10.309	10.631	11.568
Delphinidin	1.966	2.134	1.888	1.927	1.553	2.120	2.183	2.233
Syringic acid	2.607	2.756	2.503	2.566	2.321	2.829	2.999	2.973
Ferulic acid	21.324	19.781	19.096	18.594	20.909	15.627	21.758	21.759
Rosmarinic acid	25.377	27.233	23.701	28.214	27.201	21.448	24.961	25.251
Rutin	336.886	356.089	323.304	358.137	293.091	335.521	333.944	338.135
Quercetin	85.309	91.963	81.896	91.385	73.366	92.560	87.252	84.108
Gallic acid	4.545	4.189	4.020	3.937	4.427	3.728	4.569	4.733

The antibacterial effect of *E. hyemale* extracts prepared under different conditions against *S. aureus*, *E. coli* and *P. aeruginosa* was investigated by the agar well method, and it was observed that different zone diameters were obtained (Figure 1). It was determined that the zone diameters around the wells of the extracts prepared with ethanol and methanol were in the range of 14-16 mm, and the lowest concentration at which the extracts were effective was determined by the MIC test.

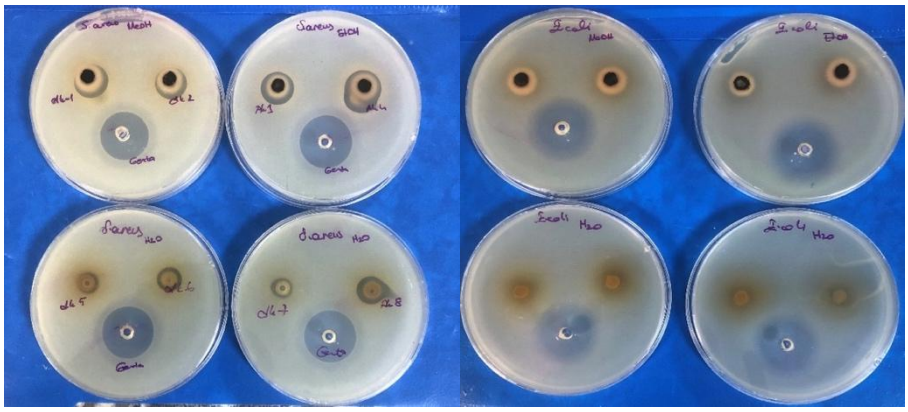

Figure 1. Agar well diffusion results of *E. hyemale* extracts against bacteria.

The MIC values of *E. hyemale* extracts prepared with different solvents are presented in Table 4. According to the findings, extracts prepared with EtOH and MeOH showed lower MIC values against all three bacterial strains compared to the water-based extract.

Table 4. MIC values (mg/mL) of extracts.

Sample Code	*S. aureus*	*E. coli*	*P. aeruginosa*
EH-E-30	0.85	0.85	6.875
EH-E-60	0.54	0.54	4.375
EH-M-30	1.05	1.05	8.43
EH-M-60	0.85	0.85	4.875
EH-W-30-1	105	52.5	26.25
EH-W-60-1	55	27.5	13.75
EH-W-30-2	125	62.5	31.25
EH-W-60-2	140	70	35

The extraction process, which is the first step in studies involving the bioactive components of plants, is crucial. Selecting the appropriate extraction method is essential to maximize the yield of extracts obtained from tissues. Extraction efficiency is influenced by several critical factors, including the extraction technique, the matrix characteristics of the plant components, the solvent used in the extraction process, temperature, pressure, and duration (Jha & Sit, 2022). The toxicity results reveal the cytotoxic effects of different extracts on L929 cells. The cell line used in this study represents healthy fibroblast cells, and IC50 values were used to measure how sensitive these cells are to the extracts. The results are given in Table 5.

IC_{50} values were determined for different extracts in the L929 cell line for 72 hours of incubation time using the MTT method. As it is known, a lower IC_{50} value indicates higher toxicity, meaning that less concentration is needed for the cells to survive. In our study, EH-W-30-2 (11.02 µg/mL) and EH-M-30 (11.38 µg/mL) had the lowest IC_{50} values and were determined as the most toxic extracts among the prepared extracts. EH-E-30 (22.37 µg/mL) and EH-M-60 (17.51 µg/mL) extracts exhibited lower toxicity than EH-M-30 and EH-W-30-2. On the other hand, EH-E-60 (123.50 µg/mL) was obtained as one of the extracts with the lowest toxicity since it had the highest IC_{50} value. In conclusion, when evaluated in terms of toxicity, some extracts (especially EH-W-30-2) exhibited highly toxic properties, while others (e.g., EH-E-60) were found to be less harmful in healthy cells.

Table 5. IC_{50} results for extracts in the L929 cell line for 72 h.

Extracts	IC_{50} (µg/mL) L929
EH-E-30	22.37
EH-E-60	123.50
EH-M-30	11.38
EH-M-60	17.51
EH-W-30-1	71.13
EH-W-60-1	68.96
EH-W-30-2	11.02
EH-W-60-2	79.28

These data are important for determining the concentrations of these extracts that can be used without damaging cell viability. Wound healing is associated with the rate of cell migration across the wounded area. In this study, the effects of different extracts on wound width were investigated. The results revealed that the rate of wound closure varied depending on the extract when different extracts were compared with the control group (Figure 2).

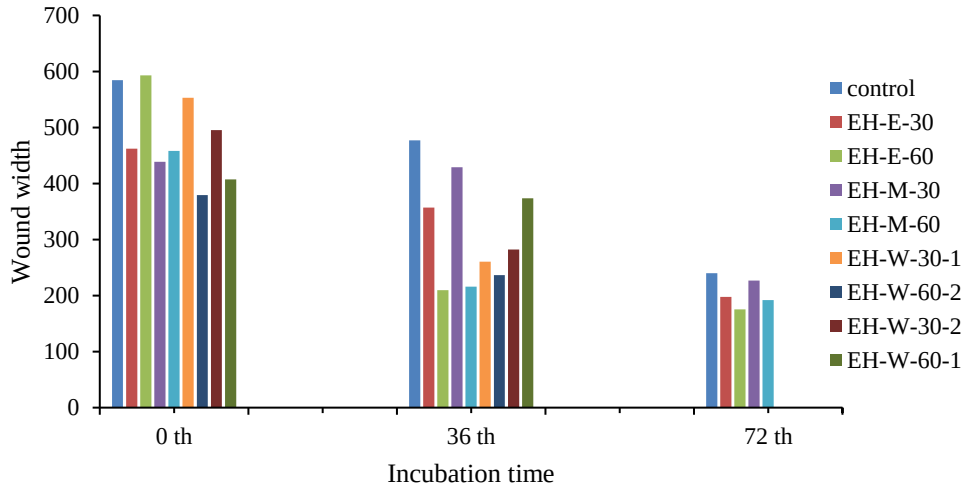

Figure 2. Wound widths vary depending on the incubation period.

At the 0th hour, the wound width in the control group was measured as 584.16 µm. Among the extracts, the initial width was measured as 460.45 µm for EH-E-30, 593.07 µm for EH-E-60, 438.71 µm for EH-M-30, 458.31 µm for EH-M-60, 553.09 µm for EH-W-30-1, 460.28 µm for EH-W-60-1, 495.31 µm for EH-W-30-2 and 379.15 for EH-W-60-2 (Figure 3). These data indicate that the initial wound width varied slightly with each extract but was generally similar.

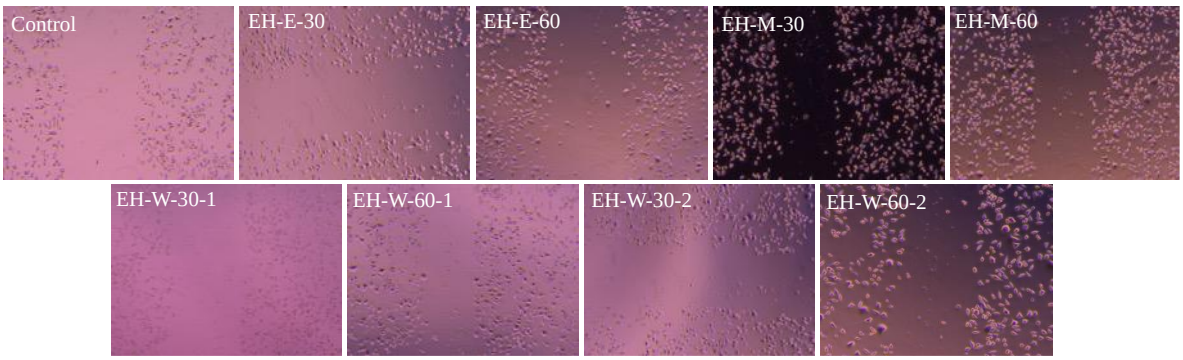

Figure 3. Wound widths at 0th hour.

At the thirty-sixth hour, the wound width decreased to 477.10 µm in the control group, indicating a certain degree of healing. At the thirty-sixth hour, the wound width reduced to 356.79 µm for EH-E-30, 209.56 µm for EH-E-60, 418.82 µm for EH-M-30, 215.82 µm for EH-

M-60, 260.61 µm for EH-W-30-1, 236.67 µm for EH-W-60-2, 282.38 µm for EH-W-30-2, and 373.41 µm for EH-W-60-1. At this stage, it was observed that some extracts, especially EH-E-60 and EH-M-60 significantly increased the rate of wound healing (see Figure 4).

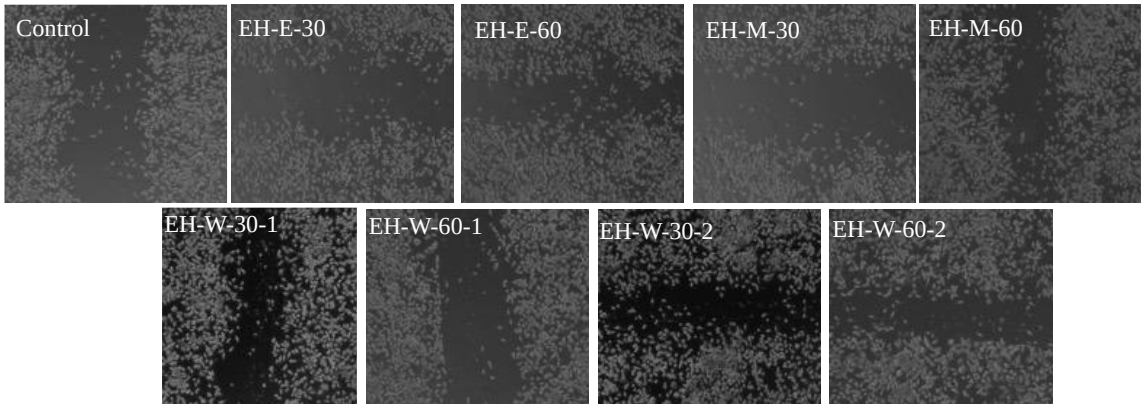

Figure 4. Wound widths at 36th hour.

Figure 5. Wound widths at 72th hour.

At the seventy-second hour, the wound width in the control group reduced to 239.64 µm. At the 72nd hour, the wound width decreased to 227.04 µm with EH-M-30, 197.69 µm with EH-E-30, 175.51 µm with EH-E-60, and 192.15 µm with EH-M-60 (see Figure 5). At 72 hours, EH-M-60 (192.15 µm) and EH-E-60 (175.51 µm) stand out among the extracts that provide the fastest wound healing. This indicates that these extracts may have positive effects on wound healing. In conclusion, compared to the control group, many of the prepared extracts provided faster wound healing, especially EH-E-60 showed a remarkable healing effect. The wound width of this extract decreased to a lower level at 72 hours compared to the control group.

The efficacy of the EH-M-60 and EH-E-60 extracts in both antibacterial activity and wound healing is higher compared to other extracts. This may be attributed to the higher concentration of phenolic compounds, particularly quercetin and rutin, present in these two extracts. In a study conducted by Irfan *et al.*, it was reported that rutin and quercetin obtained from plant extracts accelerate the wound healing process (Irfan *et al.*, 2022). These results indicate that especially EH-E-60 extracts have strong wound healing effects, increase the rate of wound closure, and therefore can be evaluated as potential therapeutic agents.

DISCUSSION and CONCLUSION

Extracts of *E. hyemale* were obtained using the ultrasonication-assisted extraction method under various extraction conditions. Ethanol, methanol, and water were used as solvents, and extractions were performed at different durations. It was observed that both the extraction time and the solvent had an effect on the extraction efficiency. Furthermore, LC-MS/MS analysis of the obtained extracts revealed that the phenolic compound content was influenced by these parameters. The highest phenolic compound content was found in the EH-E-60 and EH-M-60 extracts.

The antibacterial activities of the extracts were tested against *S. aureus*, *E. coli*, and PAO1 strains, and the extracts with higher phenolic compound content demonstrated stronger antibacterial activity.

The MIC values of *E. hyemale* extracts prepared with different solvents indicate that ethanol and methanol extracts exhibited stronger antimicrobial activity, as evidenced by their lower MIC values against all three bacterial strains compared to the aqueous extract. This suggests that solvent polarity significantly influences the extraction of bioactive compounds responsible for antimicrobial effects, with organic solvents like ethanol and methanol being more effective in isolating these constituents than water. These findings align with previous studies reporting enhanced antibacterial activity in ethanolic and methanolic plant extracts relative to aqueous preparations (Borges *et al.*, 2020; Jam *et al.*, 2021; Önem *et al.*, 2023).

Moreover, several studies have demonstrated the antimicrobial activity of *E. hyemale* extracts. For instance, Queiroz *et al.* (2014) reported that ethanolic and methanolic extracts of *E. hyemale* exhibited antimicrobial activity against *S. aureus, S. epidermidis, B. subtilis, E. coli,* and *P. aeruginosa*, with MIC values of 1.25 mg/mL (Queiroz *et al.*, 2014). Similarly, Alves *et al.* evaluated the antibiofilm, antimicrobial, and antiparasitic properties of crude *E. hyemale* extract and stem fractions against a wide range of microorganisms, including bacteria, fungi, mycobacteria, and trypanosomes, using the broth microdilution method. They found that the extracts inhibited bacterial growth at MICs ranging from 52.4 mg/mL to 3.27 mg/mL (Dos Santos Alves *et al.*, 2016). These findings from the literature are consistent with our own results, further supporting the antimicrobial potential of *E. hyemale* extracts, particularly those prepared with ethanol and methanol.

In our study, the wound healing potential of *E. hyemale* extracts was also evaluated by measuring the reduction in wound width over 72 hours. While the control group showed a decrease in wound width from 584.16 µm to 239.64 µm, treatment with the EH-E-60 extract resulted in a greater reduction, from 593.07 µm to 175.51 µm, indicating a positive effect of the extract on the healing process. These findings are consistent with the study of Aguayo-Morales *et al.* (2023), who demonstrated that a 40% ethanolic extract of *E. hyemale* significantly accelerated wound healing in diabetic rats. Their study revealed that the extract promotes healing through multiple mechanisms, including anti-inflammatory effects mediated by increased IL-10 and decreased MCP-1 levels, as well as strong antimicrobial activity against *S. aureus* and *E. coli*. Furthermore, enhanced fibroblast proliferation and collagen synthesis observed in vitro support the role of *E. hyemale* in tissue regeneration (Aguayo-Morales *et al.*, 2023). Together, these results highlight the therapeutic potential of *E. hyemale* extracts not only due to their antimicrobial properties but also through modulation of the immune response and stimulation of extracellular matrix production, validating their use as natural agents for improving wound healing.

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Declaration of Conflicting Interests and Ethics

The authors declare no conflict of interest. This research study complies with research and publishing ethics. The scientific and legal responsibility for manuscripts published in IJSM belongs to the authors.

Data Availability Statement

Research data is available and can be sent with e-mail upon request.

Authorship Contribution Statement

Firdevs Mert Sivri: Writing-original draft, Investigation, Methodology, Resources, Supervision. **Senem Akkoç:** Writing-original draft, Investigation, Methodology. **Ebru Önem:** Writing-original draft, Investigation, Methodology. **Ulaş Evren Arın**: Writing-original draft, Investigation, Methodology.

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