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Antioxidant, antiproliferative and antimicrobial activities of three lichens: *Ramalina fastigiata*, *Xanthoria parietina*, *Aspicilia intermutans*

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ABSTRACT: In this study, antioxidant, antimicrobial, antiproliferative and, cytotoxic activities of the lichen species *Ramalina fastigiata*, *Xanthoria parietina* and *Aspicilia intermutans* were investigated. It was determined that *Aspicilia intermutans* contained higher DPPH radical and ABTS cation radical scavenging activity and total phenolic substance than the other species. It was determined that *Ramalina fastigiata* had the highest iron (III) ion reducing antioxidant capacity. It was exhibited that *Ramalina fastigiata* showed antibacterial activity against *Staphylococcus epidermidis* (MIC: 312 µg/mL) and *Escherichia coli* (MIC: 156 µg/mL) strains. In addition, it was determined that *Xanthoria parietina* showed significant antiproliferative activity on the HeLa cell line. According to the obtained findings, it was determined that none of the three species showed significant toxicity on non-tumoregenic cells. The fact that none of the three species showed toxicity on healthy cell lines suggests that these species can be used for medical purposes.

KEYWORDS: *Ramalina fastigiata*; *Xanthoria parietina*; *Aspicilia intermutans*; antioxidant; antimicrobial; antiproliferation.

1. INTRODUCTION

Lichens are not organisms in their own right. They are symbiotic associations of fungi and photosynthetic algae. Lichens have a wide distribution area in the world and are found in settlements and difficult conditions from the sea to high mountains, from hot regions to the poles. Thallus develops slowly, and is found on trees, soil and rocks. They contribute to soil formation by breaking down the rocks on which they are located. However, they are negatively affected by environmental factors, especially air pollution. Some lichens disappear in crowded city centers due to atmospheric pollutants. They have a completely different structure from the algae and fungi that form them in terms of shape and lifestyle. Lichens are organisms that can be found in many places. They vary in their morphology or appearance. Crustacean lichens are lichens that usually grow on rocks, and Protoparmeliopsis muralis is an example of this. Some lichen species can also be observed to penetrate a few mm into the rock using enzymes that can dissolve rocks. This group of lichens is also called "Endolithic lichens" and *Verrucaria* species are examples of this[1,2].

Lichens have been traditionally used in Chinese medicine for fungal and systemic fungal infections of the mouth, stomach, intestines, anus, vagina, nose, ear, and skin. They have also been used as folk remedies for hair strengthening, urinary tract problems, and treating bone fractures [3].

Letharia vulpina is used for eczema and red rashes on the skin and as an anti-inflammatory. *Lobaria pulmonaria* is used as a depilatory as well as a treatment for eczema. It is also used in children's facial peeling and in the treatment of light-colored spots on the face. Many species of the genus *Cetraria*, especially *Cetraria islandica*, have a very wide range of uses. It is used in the treatment of asthma, diabetes, nephritis, lung and excretory system diseases. It is also known to be good for coughs and colds. Today, it is known that species of the genus *Cetraria* or *Usnea* are included in many throat lozenges. Species in the *Parmelia* genus are used in India as an aphrodisiac, for blood and heart diseases, stomach disorders (indigestion), bronchitis, dry throat, toothache and in general for all pains [4].

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Hippocrates recommended species in the *Usnea* genus to prevent diseases related to the reproductive organs. Today, it is used in the treatment of some gynecological diseases, as well as intestinal disorders such as diarrhea, etc. In addition, it is used as an expectorant, as a treatment for lung problems and asthma. It is also known to play a role in preventing viral diseases[5].

It has been reported that lichens contain aliphatic acids, pulvinic acid derivatives, dibenzofurans, anthraquinones and naphthoquinones compounds. Many of the secondary metabolites obtained from lichens are known to exhibit a wide range of biological effects, including antibiotic, antimicrobial, antiviral, anti-inflammatory, analgesic, antipyretic, antiproliferative and cytotoxic effects[6].

Ramalina species are most commonly used in the medical, perfumery and cosmetic fields. It is known that the *Ramalina* genus contains the usnic acid compound, and it has been recorded that this compound is used as a pure substance in creams, toothpastes, mouthwashes, deodorants and sunscreen products [7]. In previous studies on *Ramalina farinacea, Ramalina fastigiata* and *Ramalina fraxinea* species, methanol extracts of these species have been found to have significant antibacterial effects [10]. The *Xanthoria parietina* species is listed in various pharmacopoeias. This species is distributed in Australia, Africa, Asia, North America and Europe. *Xanthoria parietina* has been used to treat menstrual complaints, kidney disorders, and as a pain reliever. The color of the *Xanthoria parietina* species is due to the anthraquinone compound parietin [8]. *Aspicilia intermutans* species is known as a Mediterranean microlichen species and there are limited scientific studies on it [9].

Therefore, the aim of this study was to investigate the antioxidant, antimicrobial and cytotoxic activities of extracts from these three types of lichens (*Ramalina fastigiata, Xanthoria parietina, Aspicilia intermutans*).

2. RESULTS

2.1. Antioxidant Activity

2.1.1.Ferric reducing antioxidant activity (FRAP)

FRAP assay was performed according to the method developed by Benzie and Strain (1996) and modified slightly. The antioxidant capacity based on the ability to reduce ferric ions of the samples were calculated from the linear calibration curve and expressed as µM $FeSO_4$ equivalents per milligram (mg) of sample.

The calibration equation for $FeSO_4$ was Absorbans= 1.668 X-0.116 (R2= 0.9982).

The Ferric reducing antioxidant activity of the extracts and standard follows the order:

A.acid (2.15 µM$FeSO_4$ /0.2 mg extract) > *Ramalina fastigiata* (0.63 µM$FeSO_4$ /0.2 mg extract) > *Xanthoria parietina* (0.55 µM$FeSO_4$ /0.2 mg extract) > *Aspicilia intermutans* (0.32 µM$FeSO_4$ /0.2 mg extract)

The R. fastigiata had higher Ferric reducing antioxidant capacity than other extracts(Table 1).

2.1.2.Free radical scavenging activity (DPPH)

DPPH is usually used as a reagent to evaluate free radical scavenging activity of antioxidants. Free radical scavenging capacity of the acetone extracts from *Ramalina fastigiata, Xanthoria parietina*, and *Aspicilia intermutans* were measured by DPPH assay. The capacity to scavenge the DPPH radical was calculated using the following equation:

DPPH scavenging effect (%) = [(A0-A1) / A0)] X 100

A0 is the absorbance of the control.

A1 is the absorbance of the sample

The scavenging effect of the acetone extracts and standard with the

DPPH radical is in the following order;

A.Acid (97.89 %) > *Aspicilia intermutans* (11.92 %) > *Xanthoria parietina* (10.02 %) > *Ramalina fastigiata* (3.21 %)

The *Aspicilia intermutans* had higher DPPH free radical scavenging activity than the other extracts (Table 1).

2.1.3. ABTS radical cation scavenging activity

ABTS radical cation decolorization test is a spectrophotometric method widely used for assessment of the antioxidant activity of various substances.

ABTS radical cation scavenging capacity of the acetone extracts of *Ramalina fastigiata, Xanthoria parietina*, and *Aspicilia intermutans* were determined by the method according to Taskin et al [11].

The ABTS scavenging effect of the extracts and standard follows the order: A.acid (97.89 %)> *Aspicilia intermutans* (57.01 %) > *Ramalina fastigiate* (25.34 %) > *Xanthoria parietina* (17.15 %). *Aspicilia intermutans* exhibited stronger ABTS radical cation scavenging activity than the other extracts (Table 1).

2.1.4. Total phenolic contents

Phenolic compound contents of lichen extracts were compared by Folin–Ciocalteu method. According to the findings, the highest phenolic substance content was determined in *A.intermutans* lichen extract. It is known that there is a linear relationship between phenolic compounds and antioxidant activities. In this study, in parallel with the literature, it was determined that a.intermutans species containing high phenolic substances showed stronger ABTS and DPPH radical scavenging activity compared to other species (Table 1).

Table 1 Antioxidant activity and total phenolic contents of extracts from *R. fastigiata, X. parietina*, and *A. intermutans*

Extracts	DPPH (%)	ABTS (%)	FRAP(µM$FeSO_4$ /0.2 mg)	PC (mg GAE / 0.2 mg extract)
R. fastigiata	3.21±0.23	25.34±1.20	0.63±0.03	0.00385 ±0.0002
X. parietina	10.02±1.01	17.15±2.23	0.55±0.14	0.0019 ± 0.0003
A. intermutans	11.92±1.54	57.01±3.09	0.32±0.19	0.0057 ± 0.0003
A.asid	97.89±2.09	97.89±2.78	2.15±0.09	

2.2. Cytotoxic activity

Antiproliferative activities of lichen extracts at a concentration of 100 µg/mL were determined by MTT method on human breast (MCF-7), cervical (HeLa), colorectal (HT-29), and lung (A549) cancerous cell lines. In addition, the cytotoxicity of these extracts has been detected in the mouse embryonic fibroblast cell line (NIH3T3), which is a non-tumorogenic cell line. According to the findings, it was determined that all three species did not show significant cytotoxicity on healthy cells. In addition, it has been determined that *Xanthoria parietina* species shows significant inhibition on HeLa cancer cells proliferation. The fact that all three species did not show any toxicity on healthy cell lines suggested that these species could be used for medicinal purposes (Table 2).

Table 2 The antiproliferative and cytotoxic activities of extracts from *R. fastigiata, X. parietina,* and *A. intermutans*

Extracts (100µg/mL)	MCF-7	Hela	HT-29	A549	NIH3T3
		Cell Viablity (%)			
R. fastigiata	111.18	84.61	86.27	97.20	73.26
A. intermutans	79.23	81.91	105.95	89.34	89.58
X. parietina	89.50	38.57	86.53	93.01	94.24

2.3. Antimicrobial Activity

When the antimicrobial activities of the three lichen species were compared, it was determined that *Ramalina fastigiata* showed antibacterial activity against *S.epidermidis* (MIC: 312 µg/ml) and *E.coli* (MIC: 156 µg/ml) strains. It has been found that other lichen species do not show any antimicrobial activity (Table 3).

Table 3. The Antimicrobial activities of acetone extracts from *R. fastigiata, X. parietina,* and *A. intermutans*

Extracts	Microorganisms						
	S.aureus	*S.epidermidis*	*E.coli*	*K.pneumonia*	*P.aeruginosa*	*P.mirabilis*	*E.faecalis*
Xanthoria parietina	-	-	-	-	-	-	-
Ramalina fastigiate	-	312 µg/ml	156 µg/ml	-	-	-	-
Aspicilia intermutans	-	-	-	-	-	-	-
Levofloxacin				0,25 µg/ml			
Fluconazole				1 µg/ml			

3. DISCUSSION

In the study conducted by Soundararajan et al. in 2019, acetone extract from *Ramalina fastigiata species* was obtained and the antioxidant and antimicrobial activities of this extract were examined. According to the findings, it has been determined that acetone extract shows significant activity against *K. pneumoniae* and *Candida krusei* strains. In addition, the DPPH radical scavenging activity of acetone extract was determined as IC50: 2,052 µg/mL [10]. In our study, it did not show activity against *K. pneumonia*, but it showed activity against *S. epidermidis* and *E.coli* strains. In addition, in our study, it was determined that acetone extract showed lower DPPH radical scavenging activity, unlike the above study. This difference suggested that it was due to the fact that the place and time of gathering of the species were different [10].

In a study on *Ramalina fraxinea* and *Ramalina fastigiata* species, antioxidant activities were measured. They were tested by DPPH test, reducing power test and determination of total phenolic content. Antimicrobial activity was tested using broth microdilution method to determine the minimum inhibitory concentration. The cytotoxic activities of these two species were tested on human epithelial carcinoma (Hela), human lung carcinoma (A549) and human colon carcinoma (LS174) cells using MTT method. In the study, the tested samples showed strong free radical scavenging activity with IC_{50} values in the range of 285.45-423.51 µg/mL. In our study, this value of DPPH method at 0.5 mg/mL concentration of the extract was calculated as percentage (%) against the activity of ascorbic acid and was found to be 3.21±0.23. The total phenol concentrations in *Ramalina fraxinea* and *Ramalina fastigiata* extracts were determined as 32.63 and 33.49 µg PE/mg in this study, respectively, while the total phenolic content of *Ramalina fastigiata* extract was determined as 0.00385±0.0002 in our study. These two species were found to show strong activity against cancer cells with IC_{50} values between 24.63 and 161.37 µg/mL, while no significant activity was found in our study. In addition, the minimum measured MIC value of methyl evernate identified in these two lichen species was 0.125 mg/mL. The antimicrobial activity detected in our study against *S. epidermididis* and *E. coli* bacteria was found to be compatible with the findings in the literature. The difference between the results of the antioxidant activity and cytotoxic activity experiments in the reviewed study and the results of the experiments in our study suggests that the difference between the time and place of collection of the plant species is due to the differences [15].

The antimicrobial and antiproliferative activities of the acetone extract *of Xanthoria parietina* species were investigated and according to the findings obtained, it was determined that acetone extract showed significant antimicrobial activity against *S. aureus* strain[8]. In addition, acetone extract was found to show significant antiproliferation on the MDA-MB-231 cell line. In our study, unlike the above study, it was found that *Xanhoria parientina* species did not show antimicrobial activity, but exhibited significant inhibitory effects on the HeLa cell line, consistent with previous literature.

In a study on *Xanthoria parietina* species, antioxidant activities were tested using FCR (Folin-Ciocalteu Reagent) for total phenolic content, FRAP for iron (III) ion reducing power activity, CUPRAC for copper (II) ion reducing antioxidant power, ORAC for oxygen radical absorption capacity determination, ABTS and DPPH methods for free radical scavenging effects. While the total phenolic content determined by FCR method was 0.0078 (mg GAE / 0.2 mg extract) in the previous study, this value was 0.0019 (mg GAE / 0.2 mg extract) in our study, and iron (III) ion reduction potential was 0.1182 (µM$FeSO_4$ /0. 2 mg), while in our study this value was 0.55 (µM$FeSO_4$ /0.2 mg), IC_{50} values of DPPH and ABTS radical scavenging effects were determined as 2.7 mg/mL and 2.3 mg/mL, respectively, while in our study these values were found as 10.02% and 17.15% as % inhibition. Compared to the above study, total phenolic content was also found to be low in

our study. When the antioxidant activities examined by Frap assay method were compared, the iron (III) ion reducing power in our study was found to be higher. These differences were due to the fact that the lichens were collected at different times and from different regions [16].

No scientific studies were found in the literature review on *Aspicilia intermutans* species. For the first time, antioxidant, antimicrobial, antiproliferative and cytotoxic activities were studied in detail on this species.

4. CONCLUSION

Aspicilia intermutans and *Ramalina fastigiata* species have been observed to show significant antioxidant activity. It has been determined that the *Ramalina fastigiata* species shows strong antimicrobial activity compared to other extracts and the *Xanthoria Parietina* species shows antiproliferation in the HeLa cell line. All three lichen species were found to show no significant toxicity in the healthy cell line. Therefore, it is thought that these species can be used for medicinal purposes.

5. MATERIALS AND METHODS

5.1 Collection of lichen materials and preparation of extracts

Ramalina fastigiata, Xanthoria parietina, and *Aspicilia intermutans* species were collected by Tansu Erkan in November from Aydos Forest, Pendik/Istanbul, Turkey and identified by Assoc.Prof.Dr. Ayhan Şenkardeşler and deposited in the herbarium of Ege University. The samples extracted with acetone by maceration at room temperature until was achieved at a colourless solution. The acetone extracts were filtered and evaporated using a rotary evaporator. The extracts were decanted into vials and put into refrigeration. These crude extracts were dissolved in ethanol and used for the assessment of antioxidant activity**.**

5.2. Antioxidant activity method

5.2.1.Determination of DPPH (2,2-diphenyl-1-picrylhydrazyl) Radical Scavenging Activity

In this method, the free radical scavenging activity of the extracts is determined using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical [11]. From the extracts prepared at concentrations of 0.125–0.5 mg/mL and the standard solutions (ascorbic acid and BHT) prepared at concentrations of 5–30 µg/mL, 0.01 mL of each is taken, and 0.24 mL of 0.1 mM DPPH solution (in methanol) is added. The extracts and standard solutions to which the DPPH solution has been added are vortexed for 1 minute and then kept at room temperature in the dark for 30 minutes. The absorbances are measured at 517 nm using a 96-well microplate reader (ELISA). The control has been prepared under the same conditions by using 0.01 mL of methanol instead of the sample and standard substances. The absorbance of the control has been measured daily. The experiment has been repeated three times, and the average has been taken.

Before calculating the IC50 value, the % DPPH radical scavenging capacity is calculated using the formula given below:

% DPPH radical scavenging capacity = [(A0 – A1) / A0] × 100]

A0: The absorbance of the control solution, A1: The absorbance of the plant extracts and standard solutions. The concentration of the extract or standard substance that causes a 50% reduction in the initial DPPH concentration is defined as EC50. This value is calculated using the best-fit equation obtained by plotting the percentage of free radical scavenging activity against the tested concentrations, and the results are expressed as EC50 = mg/mL.

5.2.2.Determination of Ferric Reducing Antioxidant Power (FRAP)

The FRAP reagent is prepared by mixing 25 mL of 300 mM acetate buffer (pH 3.6), 2.5 mL of TPTZ solution (10 mM TPTZ in 40 mM HCl), and 2.5 mL of 20 mM $FeSO_4 \cdot 7H_2O$, and is then kept at 37 °C for 30 minutes. A volume of 0.19 mL of the FRAP reagent is mixed with 0.01 mL of the extract or standard (ascorbic acid), and the increase in absorbance is measured at 593 nm in the 4th minute against a reference prepared by using distilled water instead of the extract. The absorbance values of the extracts at 593 nm are compared with those obtained from the calibration curve prepared using $FeSO_4 \cdot 7H_2O$, and the FRAP value is expressed as mM $FeSO_4$/mg of extract [12].

Preparation of the $FeSO_4 \cdot 7H_2O$ Calibration Curve: In order to obtain the correct equation for $FeSO_4 \cdot 7H_2O$, a 1 mM solution of $FeSO_4 \cdot 7H_2O$ was first prepared. By diluting this solution with distilled water, solutions with concentrations of 0.4 mM, 0.2 mM, 0.1 mM, and 0.05 mM were obtained. After applying the FRAP assay to the solutions, the absorbance of the resulting colors was measured at 593 nm against the reference at the 4th minute. The assay was repeated five times, and using the obtained values, the $FeSO_4 \cdot 7H_2O$

calibration curve was plotted by applying the least squares method, and the standard regression equation was derived [12].

5.2.3.Determination of Total Phenolic Content (FCR)

0.025 mL of extracts prepared at different concentrations are taken into tubes, then 0.1 mL of Folin-Ciocalteu reagent (diluted 1:3 with distilled water) and 0.075 mL of 2% sodium carbonate solution are added. After being kept in a shaking water bath at room temperature for 2 hours, the absorbance of the resulting blue color is measured at 760 nm against a reference containing 0.025 mL distilled water instead of the extract. Total phenolic content is determined using the Folin-Ciocalteu reagent in gallic acid solutions prepared at different concentrations. A calibration curve is prepared by plotting the measured absorbances against the concentrations, and the regression equation is obtained. Based on this obtained linear regression equation, the total phenolic contents of the samples are calculated as mg gallic acid equivalents (mg GAE/g extract). The assay is repeated three times and the average is taken [11].

Preparation of the Calibration Curve for Gallic Acid: To obtain the standard regression equation of gallic acid, solutions of gallic acid are prepared at different concentrations. After applying the Folin-Ciocalteu method to the solutions, the absorbance of the resulting color is measured at 760 nm. The assay is repeated five times, and the gallic acid calibration curve is obtained by applying the least squares method to the measured values. The total phenolic contents of the extracts are determined as mg gallic acid equivalents by using the linear equation obtained from the standard gallic acid calibration curve.

5.3. Determination of cell viability

The acetone extracts was evaluated and screened against human breast cancer cell line MCF-7 (ATCC, HTB-22), human servix cancer cell line HeLa (ATCC, CCL-2), human lung cancer cell line A549 (ATCC, CRM-CCL-185), and human colorectal cancer cell line HT-29 (ATCC, HTB-38). Mouse fibroblast cell line NIH3T3 (ATCC, CRL-1658) was chosen as normal cell line. The cells were cultured in Dulbecco's Modified Eagle Medium (DMEM, Gibco, Rockville, MD, USA) supplemented with 10% (v/v) fetal bovine serum (FBS) and 1% (v/v) penicillin-streptomycin (Gibco, Rockville, MD, USA). All cell lines were maintained at 37 °C in a humidified incubator with 5% CO_2. Cell viability was evaluated using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay [13].

5.4. Determination of antimicrobial activities

Antimicrobial activity against *S. aureus* ATCC 29213, *S. epidermidis* ATCC 12228, *E. coli* ATCC 25922, *E. faecalis* ATCC 29212, *K. pneumoniae* ATCC 4352, *P. aeruginosa* ATCC 27853, *P. mirabilis* ATCC 14153 and *C. albicans* ATCC 10231 were determined by the microbroth dilutions technique using the Clinical Laboratory Standards Institute (CLSI) recommendations. Mueller-Hinton broth for bacteria, RPMI-1640 medium buffered to pH 7.0 with MOPS for yeast strain were used as the test medium. Serial two-fold dilutions ranging from 2500 mg/ml to 2.4 mg/ml were prepared in medium. The inoculum were prepared using a 16-18 h broth culture of each bacteria and 24 h culture of yeast strains adjusted to a turbidity equivalent to a 0.5 McFarland standard, diluted in broth media to give a final concentration of $5x10^5$ cfu/mL for bacteria and $0.5x10^3$ to $2.5x10^3$ cfu/ml for yeast in the test tray. The trays were covered and placed in plastic bags to prevent evaporations. The trays containing Mueller-Hinton broth were incubated at 35°C for 18-20 h and the trays containing RPMI-1640 medium were incubated 35°C for 46-50 h. The minimum inhibitory concentrations (MIC) were defined as the lowest concentration of compound giving complete inhibition of visible growth [14].

Levofloxacin and fluconazol were used as reference antibimicrobials for bacteria and yeast, respectively. Also as control, antimicrobial effects of the dimetil sulfoxid was investigated against test microorganisms. According to values of the controls, the results were evaluated.

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