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Bioactive Components and Antioxidant, Antimicrobial Activity of *Rhus coriaria*, a sumac species found in Turkey
Türkiye'de Bulunan Sumak Türlerinden Rhus coriaria Türünün Biyoaktif Bileşenleri ile Antioksidan ve Antimikrobiyal Aktivitesi

Çalışkan et al. Biological Activity of Rhus coriaria Species

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ABSTRACT

Introduction: In our study, it was aimed to analyze the antioxidant and antimicrobial activities of the extracts of the fruits of Rhus coriaria L. (sumac) species collected from Gaziantep city.

Methods: Ethanol extracts of 80% (R2) and 100% (R3) were prepared from Rhus coriaria fruits. Chemical analysis of the extracts were investigated by Liquid Chromatography-High Resolution Mass Spectrometry (LC-HR/MS) method, their antioxidant activities were investigated by 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging activity, and their antimicrobial activity was investigated using broth microdilution method.

Results: In the chemical analysis of R2 and R3 extracts, fumaric acid, an organic acid with the highest concentration, was found to be 31076.55 and 23348.37 mg/kg, respectively. While the phenolic components with the highest concentration in R2 were observed as hyperoside (622.24 mg/kg), ellagic acid (343.63 mg/kg) and p-coumaric acid (182.91 mg/kg), the phenolic components with the highest concentration in R3 were observed as ellagic acid (607.30 mg/kg), hyperoside (440.41 mg/kg) and p-coumaric acid (178.61 mg/kg). In antioxidant activities of R2 and R3 extracts, DPPH free radical scavenging activities were found to be 70.78% ± 0.002% and 11.19 ± 0.001%, respectively. Antimicrobial activities of R2 and R3 extracts were found to be 125 and <3.9 µg/ml in S. aureus strain ATCC 25923, 15.625 and 31.25µg/ml in A. baumannii strain ATCC 19606, 62.5 µg/ml in H. pylori strain ATCC 43504, 62.5 µg/ml in C. glabrata strain ATCC 2001, <3.9 µg/ml in C. albicans strain ATCC 66027, respectively.

Conclusion: The higher antioxidant activity in the R2 extract obtained from R. coriaria fruits grown in our country may be due to the higher phenolic component content compared to the R3 extract. It was thought that the more effective antimicrobial activity detected in the R3 extract may be due to the higher amount of ellagic acid compared to the R2 extract.

Keywords: Rhus coriaria, phenolic component, antioxidant activity, antimicrobial activity

ÖZ

Amaç: Çalışmamızda Gaziantep şehrinden toplanan Rhus coriaria L. (sumak) türünün meyvelerine ait ekstrelerin kimyasal analizi yapılarak, antioksidan ve antimikrobiyal aktivitelerinin incelenmesi amaçlanmıştır.

Yöntem: Rhus coriaria meyvelerinden %80 (R2) ve %100'lük (R3) etanol ekstraktları hazırlanmıştır. Ekstraktların kimyasal analizi Sıvı Kromatografi-Yüksek Çözünürlüklü Kütle Spektrometre (Liquid Chromatography-High Resolution Mass Spectrometry, LC-HR/MS) yöntemi, antioksidan aktiviteleri 1,1-diphenyl-2-picrylhydrazyl (DPPH) serbest radikal giderim aktivitesi, antimikrobiyal etkinliği sıvı mikrodilüsyon yöntemi kullanılarak araştırılmıştır.

Bulgular: R2 ve R3 ekstraktlarının kimyasal analizinde en yoğun miktarda bir organik asit olan fumarik asit sırasıyla 31076.55 ve 23348.37 mg/kg olarak saptanmıştır. R2'de konsantrasyonu en yüksek olan fenolik bileşenler hyperoside (622.24 mg/kg), ellagic acid (343.63 mg/kg) ve p-coumaric acid (182.91 mg/kg) iken, R3'de konsantrasyonu en yüksek olan fenolik bileşenlerin ellagic acid (607.30 mg/kg), hyperoside (440.41 mg/kg) ve p-coumaric acid (178.61 mg/kg) olduğu gözlenmiştir. R2 ve R3 ekstraklarının antioksidan aktivitelerinde DPPH serbest radikal giderim aktivitesinin sırasıyla %70,78 ± 0,002 ve %11,19 ± 0,001 olduğu tespit edilmiştir. R2 ve

R3 ekstraktlarının antimikrobiyal aktiviteleri; S. aureus ATCC 25923 kökeninde sırasıyla 125 ve <3.9µg/ml, A. baumannii ATCC 19606 kökeninde sırasıyla 15.625 ve 31.25µg/ml, H. pylori ATCC 43504 kökeninde 62.5 µg/ml, C. glabrata ATCC 2001 kökeninde 62.5 µg/ml ve C. albicans ATCC 66027 kökeninde <3.9 µg/ml olarak saptanmıştır.
Sonuç: Çalışmamızda ülkemizde yetişen R. coriaria meyvelerinden elde edilen R2 ekstresinde daha yüksek saptanan antioksidan aktivitenin, R3 ekstresine kıyasla fenolik bileşen içeriğinin daha fazla olmasından kaynaklanabilir. R3 ekstresinde saptanan daha etkin antimikrobiyal aktivitenin, R2 ekstresine kıyasla fazla miktarda ellagic acid içermesinden dolayı olabileceği düşünülmüştür.
Anahtar Sözcükler: Rhus coriaria, fenolik bileşen, antioksidan aktivite, antimikrobiyal aktivite

INTRODUCTION

Since ancient times, plants have been used for wellness and for the treatment of various diseases. One of these medicinal plants, the genus Rhus, which is called sumac in the regions where it grows, spreads in temperate and tropical regions, and includes more than 250 flowering plant species from the *Anacardiaceae* family. Rhus species have taken place in the treatment of many diseases in traditional treatment methods with medicinal plants in the culture of the societies in the regions where they are grown. Today, it has been reported that some Rhus species have important biological activities and nutritional values. Their important effects here are due to the large number of bioactive secondary metabolites they contain (1-3).

Rhus coriaria (sumac), which is found in many Mediterranean and Middle Eastern countries such as Lebanon, Syria, Jordan and Iran, grows naturally in Turkey, in the Mediterranean and Southeastern Anatolia. Since the dried and dark red powdered fruits of this plant have an acidic and sour taste, sumac is consumed as a flavor-enhancing spice in salads and meals (2). Besides the consumption of *R. coriaria* as a food, it has been used as a traditional medicine in the Middle East and South Asian countries for thousands of years in the treatment of various diseases, including cancer (2). While *R. coriaria* is used for wound healing, diarrhea, cold and ulcer treatment in traditional Turkish medicine, it has also been prescribed for the treatment of many illness such as liver diseases, urinary system diseases, dental diseases and high cholesterol in Arab countries. (1, 2). Similarly, *R. coriaria* was used in the treatment of respiratory diseases such as common cold in Cyprus and in the Ottoman (1).

Many therapeutic effects of *R. coriaria* such as antioxidant, anti-inflammatory, hypoglycemic, hypolipidemic activities can be attributed to its various biological properties (2). In fact, in many studies on the biological activity of *R. coriaria*, it has been reported that it has antioxidant, anti-inflammatory, anticarcinogenic, antidiabetic, antiulcer, hepatoprotective and neuroprotective effects depending on its bioactive components (1, 2). For instance, its antitumor effect has been investigated in various studies on breast cancer, cervical cancer, and colorectal cancer (1, 4-6). Particularly, phenolic components of *R. coriaria*, can interfere with biological events in the cell by scavenging free radicals, inhibiting enzymes and modulating signal transmission, with their strong antioxidant activity (3).

In addition to these reported biological activities of *R. coriaria*, the antimicrobial activity of its fruit extracts has been demonstrated against various microorganisms. Anti-bacterial effect against bacteria that cause serious clinical pictures with their ability to cause disease with their toxins and to have intracellular life mechanisms, such as *Shigella dysenteriae*, *Salmonella typhimurium*, *Escherichia coli*, as well as *Bacillus cereus*, *Yersinia enterocolitica*, *Listeria monocytogenes*, which are among the important intestinal pathogens, reported in various studies. Its effect against

Helicobacter pylori, which has been proven to be associated with gastric cancer, is remarkable. In addition these, its antimicrobial activity against potential pathogenic microorganisms, which are associated with various clinical pictures and may include some resistant strains, such as *Klebsiella pneumoniae*, *Stapyhlococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans*, has been observed in many studies (7-9).

In our study, it was aimed to analyze the chemical components of extracts obtained from *R. coriaria* fruits collected in Gaziantep region in our country and to investigate their antioxidant and antimicrobial activities.

METHODS

Supply of herbal material and preparation of extracts

In this study, extracts of dried fruits of *Rhus coraria*, which is collected from Gaziantep city, were used. Fruit samples were crushed into powder before being extracted. Solvent was added on it at a ratio of 1:10. 80% and 100% ethanol were used as solvent. The extracts were prepared by maceration method in a shaking incubator at 35°C for 24 hours. The solvents of the extracts obtained were completely removed with a rotavapor and lyophilizer, coded as R2 and R3, stored at +4°C until the experimental stage.

Chemical profile by LC-HR/MS

Phenolic components in extracts of *R. coriaria* fruits were determined by LC-HR/MS method. LC-HR/MS experiments were performed by a Thermo Orbitrap Q-Exactive ESI Mass Spectrometry system (Thermo Fisher Scientific, Waltham, Massachusetts, USA). The samples were separated on an C18 (150 x 3 mm; 3 µm) column (Fortis Technologies, UK) at 25 °C. The chromatographic conditions, particularly the composition of mobile phase and its pH, were optimized through several trials to achieve good sensitivity and symmetric peak shapes of analytes. For that purpose, at various flow rates different solvents of mixtures, such as methanol, acetonitrile, formic acid and acetic acid were tested. The best results were acquired using methanol: formic acid as the mobile phase and was applied to the gradient programme. The mobile phase was a mixture of mobile phase A (1 % formic acid solution in water) and B (1 % formic acid solution in methanol), the gradient programme of which was 0-1.00 min 50 % A and 50 % B, 1.01-3.00 50 % A and 50 % B, 3.01-6.00 0 % A and 100 % B, 6.01-7.00 min 50 % A and 50 % B and finally 7.01-10.00 min 50 % A and 50 % B. The flow rate of the mobile phase was 0.35 mL/min. The injection volume was 10 µL. The dihydrocapsaicin was used as an internal standard.

Detection of antioxidant activity

In this study, the antioxidant effect of *R. coriaria* extracts was determined by using 1,1-diphenyl-2-picrylhydrazil free radical (1,1-Diphenyl-2-picrylhydrazine = DPPH) (Sigma Aldrich, Germany) (10). The presence of antioxidant activity was evaluated to the decrease in the absorbance value of DPPH at 517 nm, proportionally. DPPH solution at a concentration of 40 µg/mL was added on the solutions of R2 and R3 extracts prepared with ethanol at concentrations of 10, 25, 50, 100 µg/mL. Ethanol was used as a control. After 30 minutes incubation at room temperature, in the dark, absorbance values were measured at 517 nm in a spectrophotometer (Synergy H1 Reader, BioTek, U.S.A). The absorbance values of the samples were evaluated against the control. Free radical scavenging activity was calculated using the following equation.

$$\text{DPPH Removal Activity (\% inhibition)} = \frac{\text{Acontrol} - \text{Asample}}{\text{Acontrol}} \times 100$$

(Acontrol: Absorbance of control, Example: Absorbance of sample)

Detection of antimicrobial activity

Standard strains used in the study

In our study, *Staphylococcus aureus* ATCC 25923, *S. epidermidis* ATCC 49461, *Enterococcus faecalis* ATCC 29212, *Pseudomonas aeruginosa* ATCC 27853, *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 49461, ATCC 700CC, *Pseudomonas aeruginosa* ATCC 27853, *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 70063, *Acinetobacter baumannii* ATCC 19606, *Helicobacter pylori* ATCC 43504, *Candida albicans* ATCC 66027 and *Candida glabrata* ATCC 2001 strains were used in the investigation of antimicrobial activity.

The standard strains were cultured in Sabouraud Dextrose Agar, 5% Sheep Blood Agar, Mac Conkey agar and Columbia agar [(10% defibrinated horse blood and supplement with Vancomycin (10 mg/L), Cefsulodin (5 mg/L), Trimethoprim (5 mg/L) and Amphotericin B (5 mg/L)] for *Candida* species, Gram-positive strains, Gram-negative strains and *Helicobacter pylori*, respectively.

Detection of antibacterial activity

In our study, MIC values of standard bacterial strains were determined by using the resazurin microplate method to determine the antibacterial activities of *R. coriaria* extracts (11). All experiments were repeated twice and streptomycin (Sigma Aldrich, Germany) was used as a standard drug. Stock solutions of the studied samples at a concentration of 1000 µg/ml were prepared with DMSO and passed through membrane filters with a diameter of 0.22 µm. 50 µl of Brucella broth (BD BBL, USA) for *H. pylori* and 50 µl of Mueller Hinton Broth (Merck, Germany) for other bacteria were dispensed into all wells of microplates. MIC range was set as 3.9-1000 µg/ml by adding 1000 µg/ml serial dilutions of the prepared solutions to the first wells of the microplates. The final concentration of streptomycin was adjusted to 83 µg/ml and serial dilutions were made by adding 50 µl to the first well. Serial dilutions were made by placing dimethyl sulfoxide (DMSO) (Sigma Aldrich, Germany) as a negative control in one column of the microplate and 50 µl of each bacteria as a positive control on another column. 3 McFarland in Brucella broth containing 10% Fetal Bovine Serum (Lonza, USA) from colonies of *H. pylori* and 0.5 McFarland standard in Mueller Hinton Broth from other strains were prepared and diluted 1:100. 10 µl of the prepared suspension was added to the wells. The plates were covered with parafilm, the microplates of *H. pylori* were incubated in a microaerophilic environment (Thermo ScientificTM OxoidTM CampyGenTM, UK) for 72 hours at 37°C, while the others were incubated at 37°C in an aerobic environment for 24 hours. After incubation, 10 µl of 33.75 mg resazurin (Sigma Aldrich, Germany) and 20% Tween 80 (Merck, Germany) dissolved in 5 ml distilled water were added to all wells, plates were left to incubate for 2-4 hours and the results were evaluated visually. The lowest concentration that prevented the color change from purple to pink was determined as the MIC value.

Detection of antifungal activity

In our study, MIC values of standard strains were determined by using the resazurin microplate method to determine the antifungal activities of *R. coriaria* extracts (11). All experiments were repeated twice and fluconazole (Sigma Aldrich, Germany) was used as a standard drug. Stock solutions of the studied samples at a concentration of 1000 µg/ml were prepared with DMSO and passed through membrane filters with a diameter of 0.22 µm. 50 µl of Mueller Hinton Broth was distributed in each well, serial dilutions of the prepared solutions were made by adding 1000 µg/ml to the first well and the MIC range was set as 3.9-1000 µg/ml. The final concentration of fluconazole was adjusted to 30 µg/ml and serial dilutions were made by adding 50µl to the first well. Serial dilutions were made by adding DMSO to one column of the microplate as a negative control and 50 µl of standard strains to another column as a positive control. Suspensions equivalent to 0.5 McFarland standard were prepared from fresh yeast colonies and diluted as a

ratio of 1:100. 10 µl of the prepared suspensions was added to the wells. Plates were covered with parafilm and incubated in an aerobic environment at 37°C for 48 hours. After the incubation, 10 µl of 33.75 mg of resazurin dissolved in 5 ml of distilled water and 10 µl of 20% Tween 80 were added to all wells, the plates were left to incubate for 12-24 hours and the results were evaluated visually. The lowest concentration that prevented the color change from purple to pink was determined as the MIC value.

RESULTS

LC-HR/MS Analysis Results

Chemical analysis of *R. coriaria* extracts was made by LC-HR/MS method and 21 components were determined. The components determined and their concentrations (mg/kg) are given in Table 1. In Figure 1, some LC-HR/MS chromatograms of R2 and R3 extracts are shown. Fumaric acid, an organic acid with the highest concentration in R2 and R3 extracts, was determined as 31076.55 and 23348.37 mg/kg, respectively. Among the phenolic compounds, the highest amount of hyperoside, ellagic acid and p-coumaric acid was detected in the R2 extract, and their concentrations were 622.24, 343.63 and 182.91 mg/kg, respectively. The phenolic components found in the highest amount in the R3 extract were ellagic acid, hyperoside and p-coumaric acid, and their concentrations were 607.30, 440.41 and 178.61 mg/kg, respectively (Table 1).

Antioxidant activity

DPPH free radical scavenging activity was investigated at four different concentrations (10, 25, 50, 100 µg/mL). The effects were compared with BHA (Butylated hydroxy anisole), which is used as a standard. At the concentration of 100 µg/mL, inhibition was observed in R2 and R3 at rates of 70.78% ± 0.002% and 11.19 ± 0.001%, respectively (Table 2). Inhibition values of standard substances and samples are shown in Figure 2.

Antimicrobial activity

The antimicrobial activities of R2 and R3 extracts on Gram-positive, Gram-negative bacteria and yeasts were investigated by broth microdilution method. Antibacterial activity of R2 extract; MIC values of *A. baumannii* ATCC 19606, *H. pylori* ATCC 43504 and *S. aureus* ATCC 25923 strains were determined as 15.625, 62.5 and 125 µg/ml, respectively. Antibacterial activity of R3 extract; MIC values of *S. aureus* ATCC 25923, *A. baumannii* ATCC 19606 and *H. pylori* ATCC 43504 strains were <3.9, 31.25 and 62.5 µg/ml, respectively. Antifungal activity of R2 and R3 extracts; MIC values of *C. glabrata* ATCC 2001 and *C. albicans* ATCC 66027 strains were determined as 62.5 and <3.9 µg/ml, respectively (Table 3).

DISCUSSION

R. coriaria (sumac), which belongs to the *Anacardiaceae* family, is one of the important species of the Rhus genus that grows in the Mediterranean region. In the regions where *R. coriaria* grows, it is used as a flavoring spice and acidifier in appetizers and meals. Although it varies according to the region where *R. coriaria* fruits are grown, it is rich in minerals such as potassium, calcium, magnesium, phosphorus, aluminum, iron, sodium and zinc, it also contains vitamins such as thiamine, riboflavin, pyridoxine, cyanocobalamin, nicotinamide, biotin and ascorbic acid (12-14). It also has many phytochemical compounds, including tannins, flavonoids, terpenoids, anthocyanins (15). When *R. coriaria* was evaluated in terms of phenolic components, it was determined that it mostly contains gallic acid, and also contains flavonoids defined as quercetin, myricetin 3-rhamnoside and quercetin 3-glucoside (16, 17). The information in the literature have shown that products with rich phenolic compounds reduce oxidative stress and the risk of chronic diseases. It has been reported that the antioxidant, antibacterial, antifungal, anti-inflammatory and anticarcinogenic activities of *R. coriaria*, which has a very rich content,

resulting from the phenolic components and organic acids it contains, can have a protective effect against various diseases (1, 2). The polarity and concentration of the solvent used in the extraction of phenolic compounds from plant materials are the most important parameters that reveal the bioactivity of the extract. In terms of human consumption, mostly hydroalcoholic (ethanol: water) extraction is more and widely preferred. Therefore, in this study, the bioactivity of the extracts prepared with 3 different concentrations of ethanol solution was evaluated (18,19).
In our study, it was determined that *R. coriaria*, whose chemical components were analyzed by LC-HR/MS, contains fumaric acid, which is one of the organic acids, in the highest amount. While the amount of fumaric acid was reported as 3.40 mg/kg in a study from China (14) and in *R. coriaria* species growing in Syria, in a study from our country, it was determined that methanol extracts contain 452.78 mg/kg and water extracts contain 180.72 mg/kg fumaric acid (20). In the study reported by Işık et al. from our country with aqueous extracts, the fumaric acid concentration of *R. coriaria* was determined as 44.78 µg/L, while in another study, fumaric acid could not be detected in the samples collected from the city of Kahramanmaraş (12, 21). In our study, the amount of fumaric acid in 80% and 100% ethanol extracts, respectively, was found as 31076 mg/kg in R2 and 23348 mg/kg in R3, which is quite high compared to other components. These differences in fumaric acid content reported in the literature may be caused by the genus of *R. coriaria*, the geographical region where it grows, the aqueous extract or the solvents such as methanol and ethanol used in the extract. In a study, the anti-inflammatory and analgesic activities of *Fumaria indica*, which contains a large amount of fumaric acid, were associated with fumaric acid, while *Rhus coriaria*, which we detected high levels of fumaric acid, may have a role in the similar effect (22). In addition, the antimicrobial activity of fumaric acid is known and it is thought that the fumaric acid concentrations of the extracts we used in our study may also contribute to the antimicrobial activity (23).
It has been reported that components such as quercetin, quercitrin, hyperoside, myricetin, kaempferol and rutin, which are in the flavonol class among flavonoids, have antioxidant, anticarcinogenic, antidiabetic, antiprotozoal, antidepressant, and hepatoprotective properties (3). The hyperoside (quercetin-3-D-galactoside) component, which has been shown to have anti-inflammatory, anticancer, antiviral effects in many studies, was found as 622.24 mg/kg in the R2 extract and 440.41 mg/kg in the R3 extract (24). *R. coriaria* has been shown to have an anti-cancer effect in several cancer types including breast and colorectal cancer, and it is one of the rare studies in which it is reported that *R. coriaria* contains isohyperoside (4-6). Investigation of the similar activity of this component, which we have detected in large amounts in regional *R. coriaria* species, can generate important data.
Phenolic acids such as chlorogenic acid, caffeic acid, p-coumaric acid, ellagic acid and salicylic acid are considered to be powerful natural antioxidants with many biological activities such as anti-inflammatory, anticancer, antimicrobial, antiallergic, antiviral, antithrombotic, hepatoprotective (3). Many activities of ellagic acid, which is an important component of fruits and vegetables, such as anti-inflammatory, antiulcerative, anticarcinogenic, antioxidant, have been reported (25). Phytochemicals such as ellagic acid are thought to function either directly as an antioxidant against the negative effects of oxidative stress or by activating cellular antioxidant enzyme systems (26). While the amount of ellagic acid in *R. coriaria* species reported from our country was 12.29 mg/kg in the ethanol extract, this component could not be detected in the aqueous extract (20). However, in our study, ellagic acid was found to be 343.63 mg/kg in R2 extract and 607.30 mg/kg in R3 extract, and their concentrations were high. It has been thought that ellagic acid, which we detected in large amounts in our samples, may have a role in the antioxidant activity of regional *R. coriaria* species. While p-coumaric acid, which is another

phenolic acid, was detected as 0.25 µg/g in *R. flexicaulis* extracts grown in Egypt, this component could not be detected in *R. coriaria* extracts in a study conducted in our country (27, 28). In our study, p-coumaric acid was detected in 80% (R2) and 100% ethanol (R3) extracts of R. coriaria for the first time in our country. The concentrations of p-coumaric acid, caffeic acid, chlorogenic acid, salicylic acid were 182.91, 7.41, 90.43, 7.67 mg/kg, respectively, in the R2 extract, and 178.61, 6.15, 75.16, 4.93 mg/kg, respectively, in the R3 extract higher than the data in the literature.

Oxidative stress results from an imbalance between production and elimination of reactive oxygen species (ROS) (2). Phytochemicals known as secondary metabolites and especially phenolic compounds have strong antioxidant activity. In recent years, it has been reported that some plant species with antioxidant activity can reduce the risk of various diseases with the effect of phenolic compounds. Due to their strong antioxidant capacity, *R. coriaria* species have been suggested for various pathological conditions (29, 30). For instance, *R. coriaria* extract has been reported to reduce UV-A-induced ROS production in HMEC-1 cells, and to block DNA damage significantly (29). Moreover, in another study, it was observed that *R. coriaria* extract inhibited the progression of skeletal muscle atrophy and created a very strong antioxidative effect in human myoblasts exposed to oxidative stress with hydrogen peroxide (30). In the relationship between ROS levels and liver damage; the protective effect of aqueous *R. coriaria* extract against hydroperoxide (CHP)-induced oxidative stress has also been demonstrated in rat hepatocytes (31).

Due to the antioxidant activity of *Rhus coriaria,* it is known to have a protective role in various health problems such as cancer, cardiovascular and neurodegenerative diseases caused by oxidative damage (2, 13). Studies have shown that antioxidant activity is proportional to the amount of phenolic component. In a study reported in 2013, DPPH free radical scavenging activities of methanol, ethanol and aqueous extracts obtained from Iraqi sumac (*R. coriaria*) were determined as 87%, 72% and 58%, respectively. In the study, it was observed that the total phenolic component concentrations were higher in methanol extracts in parallel with the antioxidant activity (32). In a study reported from Iran, the total amount of phenolic compounds in aqueous extracts of *R. coriaria* and antioxidant activity were highly correlated, and it has been reported that DPPH free radical scavenging activities were found 37%, 90%, and 96%, at 1, 2 and 4 mg/ml concentrations, respectively (33). In a study from the Kahramanmaraş region in our country, it was reported that the antioxidant activities of the samples were 73%, and the total phenolic composition was 36.38-58.66 mg GAE/g dw (12). In another study reported from our country; the antioxidant activities of aqueous and methanol extracts of sumac fruits collected from the same region with *R. coriaria* in our study were found 42% and 56%, respectively, at 100 µg/ml concentration (34). In our study, DPPH free radical scavenging activity was found 70.78% ± 0.002% and 11.19 ± 0.001%, respectively, in R2 and R3 samples at a concentration of 100 µg/mL. Higher activity may have been observed in the R2 (80% ethanol) extract due to its higher content of phenolic compounds (Table 1). It is thought that the differences in the results reported in the literature may be due to the phenolic component content and amount of the *R. coriaria*, and the solvents used in the extraction.

Increasing antibiotic resistance, a major problem in the treatment of infections. The problem of resistance is increasing rapidly due to the fact that bacteria develop new resistance mechanisms and transfer resistance genes to other bacteria. One of the important problems in the development of resistance is to trigger the resistance with the use of antibiotics and thus, to activate the resistance genes. Activated resistance genes can also be transferred from one bacterium to another by different mechanisms (35). If there is no need for antibiotic use, this will partially

contribute to the problem of resistance development. Studies have shown the antibacterial activity of essential oils, aqueous, methanol and ethanol extracts of *R. coriaria* on some species known to be pathogenic. Consumption of R. coriaria may contribute to the prevention of foodborne infections in particular. For example, antibacterial activity of *R. coriaria* has been demonstrated on bacteria such as *E. coli*, *S. aureus*, *S. enterica*, *B. cereus*, *S. dysentariae*, *Y. enterocolitica*, which can cause foodborne infections (36-38).

In a study investigating the antibacterial activity of R. coriaria, the MIC value was reported as 0.025% for a multi-drug resistant *S. aureus* strain. This research is particularly important as it shows the effect on a resistant strain. In another study with aqueous extracts of *R. coriaria*, the MIC value for *S. aureus* was found as 0.49%. In a study by Gezici et al. from our country, it was observed that the methanol extract of *R. coriaria* was more effective, and its antimicrobial activity against *S. aureus* ATCC 6538 strain was reported as 15.62 µg/ml (34). On the other hand, in the study of Ceylan et al. with methanol extracts of *R. coriaria* collected in Şırnak, the MIC values of *S. aureus* ATCC 6538 were determined as 500 µg/ml and 1000 µg/ml (39). In our study, the MIC value of *S. aureus* ATCC 25923 strain was determined as 125 µg/ml with R2 80% ethanol extract, the MIC value was determined as <3.9 µg/ml with R3 100% ethanol extract, and more effective antibacterial activity with R3 was observed, compared to the MIC values of other bacteria used in the study (Table 3).

H. pylori, an important pathogen that can colonize the gastric mucosa, is known to cause gastritis, ulcers and gastric cancer. Urease activity of *H. pylori* has primary importance in the colonization to the gastric mucosa (40). Anti-urease activity has been shown in studies investigating the enzyme inhibition activity of *R. coriaria* (41). This activity can have a negative role in the colonization of *H. pylori*. In addition, studies on the antimicrobial activity of *R. coriaria* have also been reported to be effective against *H. pylori*. In a study reported in Iran, the mean MIC value of *R. coriaria* ethanol extracts in *H. pylori* strains isolated from patients with gastritis and peptide ulcers was found to be 214.28 µg/ml (42). In another study reported from Iran, the MIC value of *H. pylori* strain produced from gastric biopsy samples was determined as 80 mg/ml and its inhibitory effect on *H. pylori* was shown (43). Similarly, in the study of Kossah et al., it was reported that *R. coriaria* extracts had an inhibitory effect against *H. pylori*, the MIC value was found to be 1000 µg/ml in *H. pylori* (9). In our study, it was determined that both R2 and R3 *R. coriaria* extracts showed an inhibitory effect (MIC: 62.5 µg/ml) in the *H. pylori* ATCC 43504 strain, and it was thought that it could contribute to the reduction of *H. pylori*-related disorders with the effect of this activity.

In our study, the MIC value of *A. baumannii* ATCC 19606 strain, which is another important pathogen, was determined as 15.625 µg/ml with R2 80% ethanol extract. The MIC value of *A. baumannii* it was determined as 15.625 µg/ml with R3 100% ethanol extract. In the study reported by Ashoori et al. with *R. coriaria* hydroalcoholic extracts the MIC value was reported as 1024 µg/ml (44).

In addition to its antibacterial activity, *R. coriaria* has also been reported to have antifungal activity in various studies It has also been shown that *R. coriaria* inhibits the adhesion of *C. albicans* to HEp-2 epithelial cells (45). In a study, the MIC value of alcoholic extracts of *R. coriaria* was reported as 1mg/ml in *C. albicans* ATCC 60192 strain (7). In the study of Gezici et al., the antimicrobial activity of methanol extract of *R. coriaria* in *C. albicans* ATCC 10231 strain was 62.25 µg. /ml (34). In our study, the MIC values of both R2 and R3 extracts in *C. albicans* ATCC 66027 and *C. glabrata* ATCC 2001 strains were found to be 62.5 and <3.9 µg/ml, respectively (Table 3). When we evaluate the antimicrobial activity that we detected in our study, it can be said that the R3 extract shows more effective antibacterial activity compared

to R2, and the antifungal activity is also similar. This activity of the R3 extract may be because it contains almost 2 times more ellagic acid, which is have antimicrobial activity, than R2 (Table 1).

Limitations of the Study

Due to economic limitations in our study, clinical bacterial strains and different solvent could not be included. New studies can be planned with these bacteria and different solvent.

CONCLUSION

As a result; in our study, it was observed that 80% (R2) and 100% (R3) ethanol extracts obtained from *R. coriaria* fruits collected from Gaziantep city in the southeast region of our country, contain high amounts of phenolic compounds. In our study, when the phenolic compound content and antioxidant activities of the extracts were examined; it can be said that the R2 extract showed higher antioxidant activity proportionally to the phenolic compound content compared to the R3 extract. However, in terms of antimicrobial activity, it was observed that the effect of the R3 extract was stronger than R2. This activity of R3 may be due to the fact that it contains more ellagic acid, which has antimicrobial activity, together with other components it contains, compared to R2 extract. In order to determine which bioactive component plays more effective role among the biological activities of *R. coriaria* and to fully understand its mechanism of action, detailed studies at the cell and protein level are needed. Evaluation of these components, which can be determined in future studies, as therapeutic potential may be possible with comprehensive clinical studies.

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Table 1. Chemical components of *Rhus coriaria* extracts (mg/kg)					
SUBSTANCE NAME	m/z	Ionization Mode	*Rhus coriaria*		U %
			R2	**R3**	
(-)-Epigallocatechin	307.0812	Positive	3.99	1.21	3.09
Chlorogenic acid	353.0878	Negative	90.43	75.16	3.58
Fumaric acid	115.0037	Negative	31076.55	23348.37	2.88
Caffeic acid	179.0350	Negative	7.41	6.15	3.74
(+)-t*rans* taxifolin	303.0510	Negative	0.39	0.39	3.35
Luteolin-7-rutinoside	593.1512	Negative	0.64	0.83	3.06
p-Coumaric acid	163.0401	Negative	182.91	178.61	3.31
Rutin	609.1461	Negative	25.17	17.55	3.07
Hyperoside	463.0882	Negative	622.24	440.41	3.46
Dihydrokaempferol	287.0561	Negative	0.51	0.50	2.86
Apigenin 7-glucoside	431.0984	Negative	9.02	6.68	3.59
Ellagic acid	300.9990	Negative	343.63	607.30	4.20
Quercitrin	447.0933	Negative	109.40	75.46	3.78
Myricetin	317.0303	Negative	56.73	8.24	4.18
Quercetin	301.0354	Negative	37.93	23.41	2.95
Salicylic acid	137.0244	Negative	7.67	4.93	1.89
Naringenin	271.0612	Negative	2.65	2.25	4.20
Kaempferol	285.0405	Negative	15.81	14.44	3.56
3'-O-methyl quercetin	315.0510	Negative	0.23	0.16	3.58
Apigenin	269.0456	Negative	0.86	0.75	2.87
Acacetin	283.0612	Negative	0.10	0.11	3.98

***m/z:** mass to charge ratio, ****U:** *measurement uncertainty*

Table 2. DPPH free radical scavenging activity of *Rhus coraria* extracts (%)			
Concentration	R2	R3	BHA
100 µg/mL	70,78 ± 0,002	11,19 ± 0,001	70,57 ± 0,002
50 µg/mL	50,05 ± 0,003	4,46 ± 0,002	50,98 ± 0,004
25 µg/mL	30,05 ± 0,003	0	27,77 ± 0,002
10 µg/mL	14,41 ± 0,006	0	11,50 ± 0,004

Table 3. Antimicrobial activity of *Rhus coraria* extracts (MIC)		
	MIC (µg/ml)	
Microorganisms	***Rhus coraria* (%80 ethanol) (R2)**	***Rhus coraria* (%100 ethanol) (R3)**
E.faecalis ATCC 29212	250	250
S.aureus ATCC 25923	125	< 3.9
S.epidermidis ATCC 49461	62.5	62.5
E.coli ATCC 25922	1000	250
P.aeruginosa ATCC 27853	125	125
K.pneumoniae ATCC 70063	125	125
H.pylori ATCC 43504	62.5	62.5
A.baumannii ATCC 19606	15.625	31.25
C.albicans ATCC 66027	62.5	62.5
C.glabrata ATCC 2001	< 3.9	< 3.9

Figure 1. DPPH free radical scavenging activity of *Rhus coraria* extracts (%)

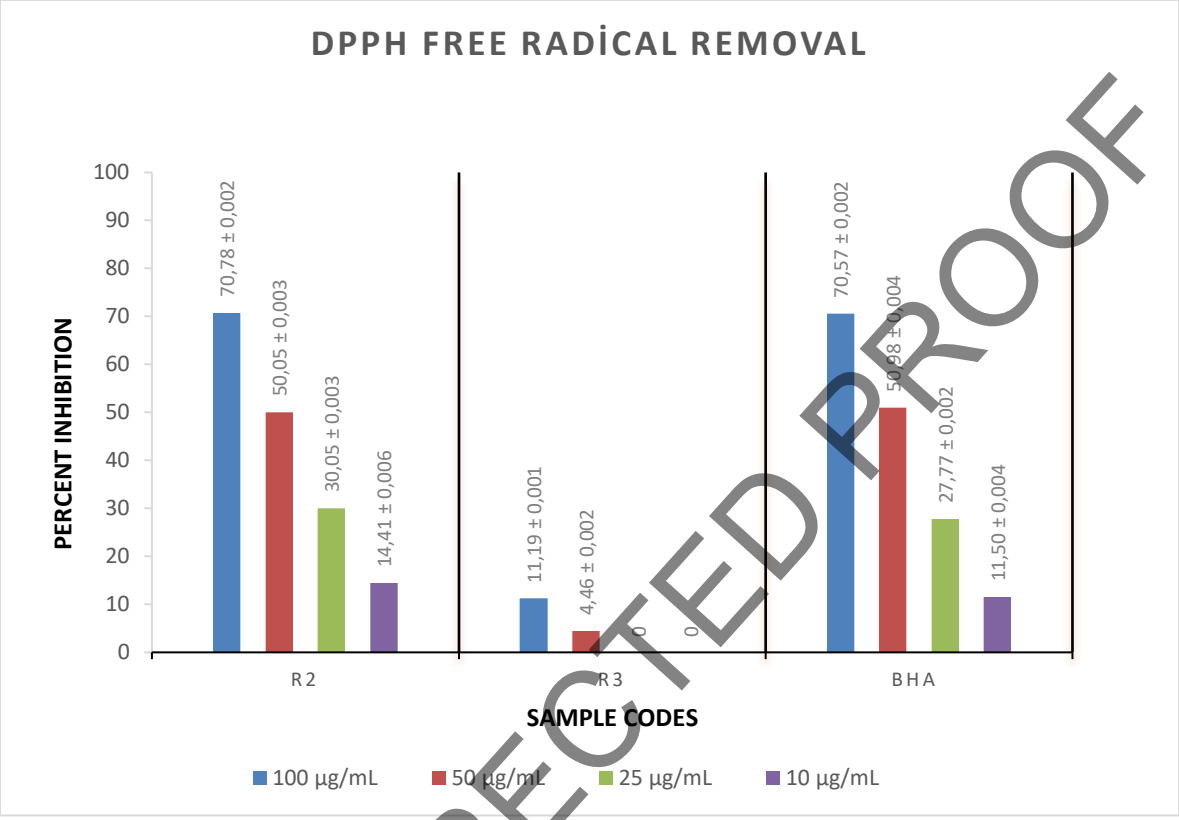

Figure 2. LC-MS/MS Chromatograms