



## Neuroprotective Effect, Antimicrobial and Antioxidant Potentials of Sumac (*Rhus coriaria* L.) Fruit Extracts

### Sumak (*Rhus coriaria* L.) Meyve Özütlelerinin Nöroprotektif Etkisi, Antimikrobiyal ve Antioksidan Potansiyelleri

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#### ABSTRACT

**I**ntroduction: *Rhus coriaria* L. (sumac) is a traditional edible-plant in the Anatolia. The leaves and fruits of sumac have been extensively used in folk medicine and alternative therapeutic approaches, because of the presence of many bioactive phytochemicals. Material and Methods: In this study, we aimed to investigate in vitro neuroprotective, antimicrobial and antioxidant properties of sumac extracts that were extracted with water, methanol, n-hexane, and dichloromethane. Results and Discussion: According to research results, almost all the tested extracts of sumac remarkable biological activities in a time and dose-dependent manner. Among the extracts, aqueous and methanolic extracts were demonstrated the highest cholinesterase inhibitory activity on both AChE and BChE enzymes, values ranging from 16.16±0.18 to 41.08±0.02% at 200µg/mL concentration. Regarding of MIC assay, all the extracts exhibited more growth-inhibitory effects against gram-negative bacteria strains than gram-positive bacteria strain, and MIC values in range of 3.9-62.5 µg/mL. In terms of DPPH radical scavenging activity, all the tested extracts demonstrated significant antioxidant capacity, methanol extract of sumac seemed to possess stronger scavenging activity (56.11±1.08% at 100 µg/mL concentration) than the other extracts. Conclusion: These findings provide contributions to medicinal uses of sumac in nervous system disorders and microbial diseases as alternative therapeutic agents, along with traditional uses of sumac.

#### Keywords

*Rhus coriaria* L., neuroprotective, antimicrobial, antioxidant.

#### Öz

**G**iriş: *Rhus coriaria* L. (sumak) Anadolu'da geleneksel olarak yenilebilen bir bitkidir. Sumağın yaprak ve meyveleri birçok biyoaktif fitokimyasalların varlığından dolayı, halk hekimliğinde ve alternatif tedavi yaklaşımlarında yaygın olarak kullanılmaktadır. Materyal ve Metot: Bu çalışmada; su, metanol, n-hekzan ve diklorometan ile ekstraksiyon yapılan sumağın nöroprotektif, antimikrobiyal ve antioksidan özelliklerinin belirlenmesi amaçlanmıştır. Bulgular ve Tartışma: Araştırma sonuçlarına göre; test edilen sumak özütlelerinin neredeyse tamamı, doz ve zamana bağlı olarak kayda değer bir şekilde biyolojik aktivite göstermiştir. Özütlelerden sulu ve metanolik olanlar, hem AChE hem de BChE enzimlerine karşı 200µg/mL konsantrasyonda %16.16±0.18 ile 41.08±0.02 arasında değişen kolinesteraz inhibitör aktivite göstermiştir. MİK analizine ilişkin olarak, tüm özütleler gram-negatif bakteri suşlarına karşı gram-pozitif bakteri suşlarından daha fazla büyüme engelleyici etki sergilemiştir ve MİK değerleri 3.9-62.5 µg/mL aralığındadır. DPPH radikal süpürücü aktivite açısından; test edilen tüm özütleler belirgin bir antioksidan kapasite göstermiş olup, metanol özütü diğer özütlelerden (%56.11±1.08, 100 µg/mL konsantrasyonda) daha güçlü radikal süpürme aktivitesine sahip olduğu görülmektedir. Sonuç: Bulgular, sumağın geleneksel kullanımının yanı sıra; sinir sistemi bozukluklarında ve mikrobiyal hastalıklarda alternatif tedavi edici ajanlar olarak tıbbi kullanımına katkı sağlamaktadır.

#### Anahtar Kelimeler

*Rhus coriaria* L., nöroprotektif, antimikrobiyal, antioksidan.

**Article History:** Received: Nov 02, 2018; Revised: Jan 21, 2019; Accepted: Jan 25, 2019; Available Online: Sep 15, 2019.

**DOI:** 10.15671/HJBC.621202

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## INTRODUCTION

The genus *Rhus* (Anacardiaceae) is represented by approximately 300 species that distributing almost all over the world. Among *Rhus* species, *Rhus coriaria* Linn, also variously known as sumac, is a wild edible-medicinal plant that is one of the most commonly used spice and appetizer in Turkey, Palestine, Persia, Central and South-West Asia, Mediterranean and Middle East [1-3]. The plant grows in temperate and subtropical areas, and widespread throughout Mediterranean and Middle East regions, including Turkey, in where it grows natively in the Mediterranean and Southeastern Anatolia [4,5]. Historically, leaves and fruits of *R. coriaria* L. were also believed as being useful for prevention of diarrhea, diabetes, ulcer, liver diseases, hemorrhoids, obesity, colitis, fever, dermatitis and hyperglycemia in the Anatolian herbal medicine. Additionally, this plant were known to have remarkable medicinal values in the treatment of sore throat, reduction of stomach pains and cholesterol in folk medicine [4-7].

Researches about the biological activity of *R. coriaria* L. have been focused on the fruit and leaf parts of this herb. Previous *in vivo* and *in vitro* studies demonstrated that sumac possesses wide range of pharmacological properties, particularly anti-fibrogenic, anti-inflammatory, antimutagenic, hypoglycemic, anti-ischemic, antimalarial, antiviral, antimicrobial, antifungal, antioxidant, antiulcer, hepatoprotective, and atheroprotective, due to presence of many natural bioactive products and secondary metabolites, e.g. tannins, gallotannins, phenolic acids, gallic acids, anthocyanins, terpenoids quercetin, isoquercitrin, myricitrin, kaempferol, apigenin, luteolin etc., which are health-promoting natural components [8-13].

Besides its rich bioactive phytochemical compositions, *R. coriaria* L. also has rich mineral contents such as Aluminum, Barium, Bromine, Calcium, Chlorine, Chrome, Copper, Iron, Magnesium, Manganese, Potassium, Lithium, Nitrogen, Nitrate, Phosphorus, Zinc, Silisium, Strontium, Lead, Titanium and Vanadium, of which, Calcium, Magnesium, Phosphorous, and Potassium are predominant elements found in sumac fruits [14,15].

In view of the comprehensive pharmacological and phytochemical properties of sumac, scientists have confirmed sumac has a great importance in both nutritional and medicinal point of views. Even though biological activities of the extracts from *R. coriaria*

L. were demonstrated before, limited works have been undertaken for analyzing the neuroprotective potentials of the various extracts of sumac according to our knowledge. On the other hand, this is the first study that has been analyzed neuroprotective potentials of sumac extracts combined with antimicrobial and antioxidant activities using different assays.

## MATERIALS and METHODS

### Collection and Authentication of Plant Material

The fruits of *R. coriaria* L. were collected during the month of July 2017 from Kilis and Gaziantep, located in South-eastern part of Turkey. Plant material identified by N. Sekeroglu, and a voucher specimen (with number KIYUHERB085) was deposited in the herbarium of Biology Department at University of Kilis 7 Aralik, Turkey.

### Preparation of Crude Extracts

Air-dried and powdered fruits of *R. coriaria* L. (50 g) were extracted with 250 mL of different solvents including water, methanol (70%), n-hexane and dichloromethane for 2 days at the room temperature. The extracts were filtered, and the methanol, n-hexane and dichloromethane phases were then removed by using a rotary evaporator (Sigma Aldrich, USA), while the water extracts were freeze-dried. All the extracts were stored at +4°C until analyzed. Extraction yields of the water, methanol, n-hexane, and dichloromethane of the fruits were determined as 14.08%, 9.20%, 5.13%, and 1.85% (w/w%), respectively.

### *In vitro* Enzyme Inhibitory Assays

Neuroprotective activities of the extracts on AChE and BChE were evaluated by a slightly modified spectrophotometric method of Ellman et al. [16] Electric eel AChE (Type-VI-S, EC 3.1.1.7, Sigma, St. Louis, MO, USA) and horse serum BChE (EC 3.1.1.8, Sigma, St. Louis, MO, USA) were used, whereas acetylthiocholine iodide and butyrylthiocholine chloride (Sigma, St. Louis, MO, USA) were employed as substrates of the reaction, respectively. 5,5-Dithio-bis(2-nitrobenzoic) acid (DTNB, Sigma, St. Louis, MO, USA) was used for the measurement of the anticholinesterase activity. All reagents and conditions were same as described in our previous researches [17,18]. Percentage of inhibition of AChE/BChE was determined by comparison of rates of reaction of samples relative to blank (ethanol in phosphate buffer pH = 8). All the assays were carried out in triplicate, and galanthamine (Sigma, St. Louis, MO, USA) was used as the reference drug.

### Microorganisms

Antimicrobial activity was evaluated against to three bacterial organisms as *Escherichia coli* (ATCC 25322), *Staphylococcus aureus* (ATCC 6538), *Pseudomonas aeruginosa* (ATCC 15442), and one fungal organism as *Candida albicans* (ATCC 10231). Streptomycin (antibiotic) and Fluconazole (antimycotic) were used as positive controls. The bacterial strains were inoculated to Mueller Hilton Agar and Eosin Methylene-blue Lactose Sucrose Agar (MHA, EMB, Merck, Germany), and the fungal strain inoculated to Sabourand Dextrose Agar (SDA, Merck, Germany).

### In vitro Antimicrobial Activity

Antimicrobial MIC (Minimum Inhibitory Concentration) assay was performed using the microdilution method in sterile 96 microplates by described Sarker et al. [19] previously. All the plates had positive controls: Streptomycin for bacteria and fluconazole for yeast with a concentration range of 0.49-1000 µg/mL. The plates were conducted in triplicate for each organism, and incubated 37°C for 18-24 h for bacteria, while 30°C 48 h for yeast.

### In vitro Antioxidant Assay

Free radical scavenging activities of the sumac extracts were determined by microplate DPPH assay according to method described by Molyneux [20] and Gezici et al. [21] with some modifications. Firstly, each extract was solved in methanol with different concentrations starting from 12.5µg.mL<sup>-1</sup> to 100µg.mL<sup>-1</sup>, and then diphenyl-2-picryl-hydrazil (DPPH, Sigma Aldrich, St. Louis, MO, USA) was dissolved in methanol for preparation 1 mM DPPH solution. Each well contained 200 µL of extract solution and 1 mL of DPPH solution, the microplates were shaken gently and incubated at room temperature for 30 min in the dark, and then the absorbance value was read at 517 nm using a spectrophotometer in triplicate.

The inhibition of the DPPH scavenging activity was calculated as below:

DPPH scavenging activity in percentage =  $(1 - A_{517} \text{ of sample} / A_{517} \text{ of control}) \times 100$ , where  $A_{\text{control}}$  is the absorbance of all the reagents except the test sample,  $A_{\text{sample}}$  is the absorbance of the extracts. Ascorbic acid was used as the standard antioxidant. A linear regression analysis was used to determine IC<sub>50</sub> values (scavenge 50% of the DPPH radicals) of the extracts.

### Statistical Analysis

All the assays were conducted in triplicate, and three different microplate wells were used for each concentration. The results were expressed as mean and standard deviation values (mean ± SD). Statistical differences between the references and the sample groups were evaluated by ANOVA (one way). Correlations were carried out using the correlation and regression in the EXCEL programme. Differences between groups were considered as significant when a P-value was set at 0.05, and very significant when a P-value was set at 0.01.

## RESULTS and DISCUSSION

### In vitro Enzyme Inhibitory Results

The extracts obtained from the fruits of *R. coriaria* L. were also evaluated for their inhibitory activities on AChE and BChE at 25, 50, 100, and 200 µg.mL<sup>-1</sup> concentrations, using galanthamine as the reference drug are given in Table 1.

According to the results of enzyme inhibitory assays, sumac was found to have protective effects against the both of the enzymes at the tested concentrations, in which the water extracts of sumac were the most potent neuroprotector with the inhibition values of 28.62±1.04% (p<0.01) on AChE and 41.08±0.02% (p<0.01) on BChE at 200 µg.mL<sup>-1</sup> (Table 1). On the other hand, the water extract exhibited the highest inhibitory activity, and the inhibitory activity of this extract was followed by methanol extract (16.16± 0.18% on AChE and 33.64±0.18% on BChE). Among the tested extracts, the n-hexane extract was exerted 11.48±0.06% and 7.76±2.06% the lowest enzyme inhibition on AChE and BChE, respectively. Additionally, the dichlorometane extracts of sumac remained inactive against the mentioned enzymes (Table 1).

As previously reported that antioxidants have neuroprotective and neuroregenerative functions, by reducing or reversing cellular damage and by slowing the progression of neuronal cell loss. Likewise, the combination of antioxidants activity and neuroprotective potentials of the herbal extracts is known to be associated with fighting neurodegenerative disorders such as such as optic neuropathies, glaucoma, Alzheimer's and Parkinson's diseases [17,21,22]. It can thus be argued that the neuroprotective activity

**Table 1.** Inhibitory activity of the extracts against AChE and BChE at 200 µg.mL<sup>-1</sup>.

Extract type	Acetylcholinesterase (AChE)	Butyrylcholinesterase (BChE)
	(Inhibition % ± SD)	(Inhibition % ± SD)
Water	28.62 ± 1.04**	41.08 ± 0.02**
Methanol	16.16 ± 0.18**	33.64 ± 0.18**
n-Hexane	11.48 ± 0.06*	7.76 ± 2.06**
Dichlorometane	— <sup>b</sup>	— <sup>b</sup>
Galanthamine <sup>a</sup> (at 100 µg.mL <sup>-1</sup> )	90.18 ± 1.04	84.02 ± 1.06

The results are given as the mean value ± standard deviation (n = 3).

<sup>a</sup>Galanthamine; reference for AChE and BChE inhibition.

<sup>b</sup>No inhibitory activity.

\*p value of < 0.05; \*\*p value of < 0.01

of the sumac extracts correlates directly with the demonstrated presence of powerful free radical scavenging activity.

### In vitro Antimicrobial Results

The results of antibacterial and antifungal activities for the extracts of *R. coriaria* L. fruits against *E. coli*, *P. aeruginosa*, *S. aureus* and *C. albicans* were summarized in Table 2.

All the extracts of sumac demonstrated more inhibitory effects against gram-negative bacteria strains (*E. coli* and *P. aeruginosa*) than gram-positive bacteria (*S. aureus*) in terms of bacterial growth. Our results are compatible with previous reports that gram-negative strains were found more sensitive than gram-positive bacteria strains [23,24]. However, the lowest antibacterial activity was determined with the dichloromethane extracts of *R. coriaria* L. against almost all bacteria strains with 62.5 and >1000 µg/mL MIC value, the methanol extracts of *R. coriaria* L. demonstrated high growth inhibitory effects against both gram-negative and gram-positive microorganisms from 3.9 to 62.5 µg.mL<sup>-1</sup> MIC value. Among all other bacteria strains, the

highest antibacterial activity was found against *E. coli* with MIC values of 3.9 µg/mL, while, the lowest antibacterial activity was found against *S. aureus*, with MIC values of 500 µg/ mL, in comparison to streptomycin (MIC= 0.49–3.90 µg/mL) as a positive control. Although, the extracts of sumac showed stronger antibacterial activities to all tested strains, they had middle antifungal activity to *C. albicans*, among the extracts the methanol and water extracts showed more anti-yeast activity than the other extracts with 62.25 µg.mL<sup>-1</sup> and 250 µg/mL MIC value, comparing with fluconazole (MIC= 1.95 µg/mL) as positive control. The antimicrobial potential of the extracts of sumac can be presented as methanol > water > n-hexane > dichloromethane. The methanol extracts of sumac proved to be the most potent one; MIC values range for 3.9–62.25 µg/mL for bacteria strains and 62.25 µg.mL<sup>-1</sup> for yeast. These results indicate that most of flavonoids and derivatives such as myricetin, quercetin, kaempferol etc. as well as terpenes such as carvacrol, α-terpineol, β-caryophyllene alcohol etc. found in sumac may possess good potential as antimicrobial agents [1,25,26].

**Table 2.** Antibacterial and antifungal activities of the extracts of *R. coriaria* L. as MIC (µg.mL<sup>-1</sup>) values.

Sumac Extracts	MIC (µg.mL <sup>-1</sup> )			
	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>S. aureus</i>	<i>C. albicans</i>
Water	7.81	31.25	125	250
Methanol	3.9	15.62	62.25	62.25
n-Hexane	31.25	62.5	250	500
Dichloromethane	62.5	125	500	>1000
Streptomycin <sup>a</sup>	0.49	1.95	3.90	— <sup>c</sup>
Fluconazole <sup>b</sup>	— <sup>c</sup>	— <sup>c</sup>	— <sup>c</sup>	1.95

All the data are presented as the mean values of triplicates for each microorganism (n=3).

<sup>a</sup>Streptomycin; standard antibiotic, positive control.

<sup>b</sup>Fluconazole; standard antimycotic, positive control.

<sup>c</sup>No inhibitory activity.

**Table 3.** DPPH radical scavenging activity (%) of the extracts from *R. coriaria* L.

Extracts	% Inhibition of DPPH ± SD			
	12.5 µg.mL <sup>-1</sup>	25 µg.mL <sup>-1</sup>	50 µg.mL <sup>-1</sup>	100 µg.mL <sup>-1</sup>
Water	20.42 ± 0.03**	23.01 ± 0.03*	26.72 ± 0.05**	42.02 ± 1.01*
Methanol	21.34 ± 0.04*	30.58 ± 0.04*	39.98 ± 0.07**	56.11 ± 1.08**
n-Hexane	18.37 ± 0.03*	20.02 ± 0.05**	2.47 ± 0.07**	35.95 ± 0.08*
Dichloromethane	16.12 ± 0.02**	19.13 ± 0.04**	22.35 ± 0.06**	29.47 ± 0.06**
AA <sup>a</sup>	23.21 ± 0.03	25.43 ± 0.03	30.96 ± 0.06	45.48 ± 1.20

The results are given as the mean value ± standard deviation (n = 3), and the data are expressed as percentage of inhibition

<sup>a</sup> AA; Ascorbic acid, commercial standard

\*p value of < 0.05; \*\*p value of < 0.01

### **In vitro Antioxidant Results**

The potential antioxidant activities of the extracts obtained from sumac were determined by DPPH radical scavenging assay. The DPPH activity results of the extracts at different concentrations starting from 12.5 µg.mL<sup>-1</sup> to 100 µg.mL<sup>-1</sup> were shown in Table 3 and the values were compared with ascorbic acid.

According to data presented in Table 3, all the extracts of sumac showed powerful superoxide radical scavenging and antiradical activities against DPPH in a concentration-dependent manner and significantly different (p<0.01) by when compared with ascorbic acid, a commercial standard antioxidant. The high DPPH radical scavenging activity determined for the methanol extract as 56.11±1.08% (p<0.01) at 100 µg.mL<sup>-1</sup> concentration. It is followed by the water and n-hexane extracts 42.02±1.01% and 35.95±0.08% (p<0.05) at 100 µg.mL<sup>-1</sup> concentration, respectively. In this assay, dichloromethane extract showed the weakest scavenging activity. The values obtained from DPPH assay are comparable with well-known antioxidant, AA (45.48 ±1.20%) which was used as positive control.

The anthocyanin, hydrolyzable tannins and gallic acid derivatives found in sumac most likely to be responsible for powerful antioxidant activity. It is probably that the extracts of sumac inhibit the production of reactive oxygen species that have potential to damage cells, and the degradation of nucleic acids and other organic compounds are prevented by the polyphenolic active constituents of *R. coriaria* L. [3,8,10,26].

### **CONCLUSIONS**

Consequently, different sumac extracts have shown significant effects on decreasing growth of microorganisms and inhibition of the AChE and BChE

enzymes, which are linked to neurodegenerative disorders. As can be seen from the data presented in this research, the extracts have been found to have strong neuroprotective and antioxidants effects in a time and concentration dependent manner, even at lower concentration and minimum exposure time. These findings suggest the consumption of sumac has the potential in the prevention of some disorders as natural sources for antioxidant, antimicrobial, as well as enzyme inhibitory agents. The obtained results could support the widespread uses of sumac in health, nutrition, and pharmacology and as a source of functional ingredients. Additional studies should be conducted to identify which bioactive phytochemical(s) are responsible for these wide ranges of biological effects actually, and should be investigated the molecular mechanisms underlying the potential effects of sumac.

### **Acknowledgments**

The author gratefully acknowledges the support and technical assistance of the Kilis 7 Aralık University, Central Laboratory. The author would like to thank Prof. Dr. Nazim Sekeroglu for his kind contribution of collecting and identifying the plant material. The abstract of the manuscript had been presented as an oral presentation in The Third International Mediterranean Symposium on Medicinal and Aromatic Plants (MESMAP-3) in Girne-T.R.N.C. in 2017.

### **Conflict of interests**

There is no conflict of interest.

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