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In vitro Efficacy of Sumac (*Rhus Coriaria*) Extracts Against *Leishmania tropicana* and *Leishmania mexicana*: A Preliminary Study from Turkiye

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Abstract

Objective: Cutaneous leishmaniasis (CL) is a common clinical manifestation of leishmaniasis. Here, *the in vitro* anti-leishmanial efficacy of sumac extracts was tested for the first time on both *Leishmania (L.) tropica and L. mexicana* isolates using *Rhus (R.) coriaria* plant, which was collected in western Anatolia.

Materials and Methods: The dried and powdered fruits of *R. coriaria* were macerated in acetone, ethyl alcohol, and ethyl alcohol-water mixture at room temperature for two days. The pooled extracts were evaporated under reduced pressure and lyophilized form for the study. Isolates of *L. tropica* and *L. mexicana* in Acibadem University R&D Laboratory were initially thawed and cultivated in NNN medium. Assessments were made using the haemocytometer and MTT methods at 24 and 48 h, compared with meglumine antimoniate as the control group.

Results: For *L. tropica*, the effective concentration ranges of the extracts and the infusion were found to be 578.13-289.06 µg/mL and 289.06-144.53 µg/mL, respectively. For *L. mexicana*, the ranges were found to be 289.06-144.53 µg/mL and 144.53-72.27 µg/mL, respectively. It was shown that all extracts of *R. coriaria* were effective against both *L. tropica* and *L. mexicana* in higher doses, compared to meglumine antimoniate.

Conclusion: An interesting finding was that higher sumac doses were required to eliminate *L. tropica* of the Old World, compared to *L. mexicana* of the New World. In addition, the aqueous alcohol extract showed efficacy that lasted for 48 h in half doses compared to others in *L. tropica*. Further assessments for both the identification of the active compounds within *R. coriaria* and their efficacy *in vivo* are planned.

Keywords *Leishmania* · Cutaneous leishmaniasis · Sumac · *Rhus coriaria*

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INTRODUCTION

Leishmaniasis is a common parasitic disease in the tropical and subtropical regions of the world, which is caused by flagellated protozoa of the *Leishmania* genus and transmitted by the sandflies (*Phlebotomus* sp. in the Old World and *Lutzomyia* sp. in the New World) (1). It appears with different clinical manifestations in humans, which are mainly cutaneous form (cutaneous leishmaniasis-CL) and visceral form which may go deadly in left untreated and the mucocutaneous form that is mostly limited in South America. Leishmaniasis is currently endemic in 99 countries today, with around 1.2 million reported cases, and CL constitutes almost 70% of all cases in the world, annually (1-3). There has been a constant increase in the incidence of leishmaniasis in many parts of the world lately, due to many factors including the refugee problem, global warming-associated longer survival of vectors in nature and expansion of the neighbourhoods to the original habitats of arthropods (4). Therefore, changes in environmental factors, vector-parasite as well as parasite-host interactions may all cause alterations in the epidemiology of leishmaniasis in many regions of the world (1, 4).

Today, it is documented that CL cases are predominantly caused by *Leishmania (L.) tropica* in the Old World and *L. mexicana* in the New World (3, 5). Skin lesions start with a small papule after the bite of a sandfly, which gradually turns into a painless nodule and ulcer overlaid by a large crust. These lesions may shrink in time even without a treatment but leave a remarkable scar tissue (5). It has also been reported that the presence of *Leishmania* virus inside the causative *Leishmania* species may aggravate the clinical manifestation of CL (6). Therefore, it is essential to apply anti-leishmanial therapy on CL lesions over 2 cm. Pentavalent antimonial compounds have long been used as the first-line agents in leishmaniasis treatment; however, there is an emerging resistance against them and their efficacy has declined in many endemic regions, such as India (4, 5). Thus, new drug trials have been conducted in many laboratories around the world to offer new options for leishmaniasis treatment, using both natural and synthetic compounds.

It is estimated that there are almost 250,000-500,000 medicinal plant species in the world, but only 6% of them have had their biological activities evaluated (7). Today, clinical trials and empirical studies on medicinal plants have been conducted in different parts of the world, especially in Asian countries (8-11). Anatolia is rich in medicinal plants, and many of them have been used in traditional medicine for centuries (10). Among them, sumac (*Rhus (R.) coriaria* L.) has been used traditionally as a spice and a flavouring agent in Anatolia, while it has also been used as a medicine owing to its anti-oxidant, anti-inflammatory, hypoglycemic, hypolipidemic and anti-microbial activities (10-12). In addition to its use as a culinary herb and tanning agent in Mediterranean countries, sumac has also been used for thousands of years as a traditional medicine for the treatment of several diseases, including cancer. Lately, its anti-parasitic activities on *L. major* were demonstrated as well (13). However, more studies are required to test its efficacy on leishmaniasis treatment.

In the present study, the anti-leishmanial efficacies of different extracts and the infusion form of *R. coriaria* were tested *in vitro* against both *L. tropica* and *L. mexicana*, the leading causative agents of CL in the Old and the New World, respectively.

MATERIALS AND METHODS

***Leishmania* Isolates:** The *L. tropica* isolate was initially isolated from a CL patient in Manisa province, stored in liquid nitrogen in the Parasite Bank located in Manisa Celal Bayar University, Faculty of Medicine, and confirmed as *L. tropica* after species-specific polymerase chain reaction (PCR) (MHOM/AZ/1974/SAF-K27). The *L. mexicana* isolate used in the study was initially purchased from ATCC (MNYC/B7/62/M379). Both species were kept at -80°C in Acibadem University's R&D Lab until the day of the trial. A total of $1x10^8$/mL of *L. tropica* and *L. mexicana* promastigotes were used during the assessments. Both isolates were removed from the liquid nitrogen tank under appropriate conditions, and after viability control, they were inoculated first in NNN medium and then in RPMI-1640 medium, supplemented with 15% fetal bovine serum (FBS), 1% penicillin-streptomycin (penicillin, 10,000 units/mL-streptomycin, 10 mg/mL) and 0.2% gentamicin (50 mg/mL). Promastigote reproduction was checked on consecutive days and following the detection of a minimum of 10 promastigotes in each microscopic field, the FBS content was dropped to 10% (14). Cultures were kept in an incubator at 25°C.

Plant Material: The fruits of fresh sumac plant samples were collected on the 5th of September 2023, in Kusadasi, a county located 110 km on the south of Izmir province in western Anatolia (Figure 1). The remaining plant samples are kept in the Herbarium of Ege University Faculty of Pharmacy Department of Pharmacognosy in Izmir (Herbarium No: 1672). The fruits were collected and identified by Prof. Dr. Cenk Durmuşkahya. Grinded sumac samples were transferred to the R&D Laboratory of Acibadem University Faculty of Pharmacy for the preparation of the alcohol, water-alcohol, acetone and infusion extracts for the study. Here, the air-dried and powdered fruits of *R. coriaria* (130 g) were macerated with acetone (1500 mL), EtOH (1500 mL), and the mixture of

EtOH:H_2O (1:1) (1500 mL) separately at room temperature for 2 days. The filtered extracts were evaporated under reduced pressure and lyophilized to obtain the crude extracts (acetone: 35.31 g, yield 27.1%; EtOH: 33.15 g, yield 25.5%; EtOH:H_2O: 19.8 g, yield 19.8%). Moreover, infusion of the *R. coriaria* was also prepared from 2 g of plant material with 100 mL of freshly boiled water, representing the typical quantity consumed by tea drinkers and lyophilized (5 g, yield 25%).

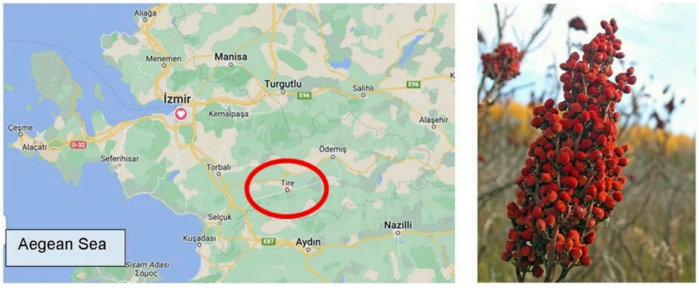

Figure 1. Location of Kusadasi County in western Anatolia where the sumac samples were collected

Application of the *In vitro* Assessments: Following the preparation of *R. coriaria* extracts and both *L. tropica* and *L. mexicana* promastigotes (1x10^8/mL each), they were mixed and incubated at room temperature in different test plates. Assessments were made using the haemocytometer and MTT methods as described at 24 and 48 h, in comparison with meglumine antimoniate as the control drug (concentration range: 300-0.19 µg/mL), the primary choice in leishmaniasis treatment today. All chemicals and references used in the trials were purchased from Sigma Chemical Co. (St. Louis, MO, USA). The dilutions used in the *in vitro* test were calculated according to the amount of *R. coriaria* content in the extracts and were assessed within the range of 18.07 µg/mL and 2312.48 µg/mL, according to the preliminary assessments.

Statistical Analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). The results were assessed by Student's t-test and false discovery rate (FDR) correction was performed during the assessments. Statistical differences identified as $p<0.05$ were considered significant.

RESULTS

The findings of the assessments are presented in Table 1. For *L. tropica*, the effective concentration ranges of the extracts and the infusion were found to be 578.13-289.06 µg/mL and 289.06-144.53 µg/mL, respectively. For *L. mexicana*, the ranges were found to be 289.06-144.53 µg/mL and 144.53-72.27 µg/mL, respectively. The effective concentration values of the control agent, meglumine antimoniate, were within the range of 25-12.5 µg/mL for both *L. tropica* and *L. mexicana* strains at the same time points.

Table 1. Activity of *R. coriaria* extracts on *L. tropica* and *L. mexicana* at the 24th and 48th hours

Type of the Sumac Extract	24th Hour (µg/mL)		48th Hour (µg/mL)	
	L. tropica	*L. mexicana*	*L. tropica*	*L. mexicana*
Ethyl Alcohol	578.13	144.53	289.06	72.27
Aqueous Alcohol (1:1)	289.06	144.53	144.53	72.27
Acetone	578.13	144.53	289.06	72.27
Infusion	578.13	289.06	289.06	144.53
Positive control (meglumine antimoniate)	25.0	25.0	12.5	12.5

DISCUSSION

The incidence of CL has been on the rise, not only in the old but also in the new World. This is mainly due to environmental factors such as global warming and human activities such as the global refugee problem and increased housing in rural regions where people are exposed to vectors more often (4). In addition, the causative agents of leishmaniasis, the *Leishmania* species may go hybridized to adapt to these changing environmental conditions in nature, including the change in vectors; this hybridization process may complicate the diagnosis and treatment of leishmaniasis cases as the available diagnostic methods and/or treatment options may become ineffective.

Pentavalent antimonial drugs, developed in the 1940s, are still the primary agents of leishmaniasis treatment in many regions of the world (5). Yet, emerging resistance in leishmaniasis against these antimonial compounds is a potential threat to clinical cases. Indeed, alternative drugs such as amphotericin B and pentamidine, which are preferred mostly for visceral infections, are reported as highly toxic for many patients (3). Therefore, there is an urgent need for new and effective drugs for leishmaniasis treatment.

Natural compounds are the primary sources of research in leishmaniasis treatment studies (8). Almost one of each three approved drugs in the market are natural products or semi-synthetic derivatives, while 30% are currently the synthetic molecules based on natural products or pharmacophores developed from natural compounds (15). It is noteworthy that 65% of the 15 anti-parasitic drugs approved by health authorities between 1981 and 2006 were natural products or their derivatives.

In different cultures and countries, medicinal plants have been used to treat parasitic diseases, including leishmaniasis

(2). Plant derivatives or extracts could provide valuable sources for new medical agents and for anti-leishmanial activity testing, which showed promising results (2, 4). Sumac (*R. coriaria*) is one of these important plant species widely used as a spice and medicinal plant in Turkiye.

R. coriaria belongs to the Anacardiaceae family and is found in the temperate and tropical regions of the world. Today, the increasing awareness of the positive effects of sumac on human health is boosting its consumption (10, 11). Sumac contains various compounds including organic acids, proteins, essential oils, vitamins, and minerals, and it may exert strong anti-microbial and anti-cancer activities in varying degrees through its different extracts (8-10). In addition, *R. coriaria* has anti-oxidant properties, as it is rich in gallic acid and its derivatives, which make it an important substance for the food industry as a natural anti-microbial (5, 10-13).

Despite the presence of many studies in the literature that indicate the anti-bacterial and anti-oxidant properties of *R. coriaria*, the number of studies that show its anti-leishmanial activity is currently limited. In a study conducted by Camacho et al. (2003), methanol extracts obtained from the leaves, bark, and seeds of *R. aucheri* Boiss were reported to be effective against *L. donovani* at concentrations of 55.85 µg/mL, 171 µg/mL, and 141.87 µg/mL, respectively, with high selectivity (SI=2.55) (8). Similarly, a recent study by Ashoori et al. (2020) extensively evaluated the anti-leishmanial and anti-bacterial potential of the hydroalcoholic extract of *R. coriaria* fruits *in vitro*. This study demonstrated a pronounced leishmanicidal effect of the extract, particularly against *L. major* promastigotes and amastigotes, with IC_{50} values of 147 µg/mL and 233 µg/mL, respectively (13). In recent years, nanotechnological approaches have emerged as promising alternatives for treating *Leishmania* infections (16). In this context, the green synthesis of haematite (Fe_2O_3) nanoparticles using *Rhus punjabensis* has been achieved, with the nanoparticles exhibiting free radical scavenging, anti-oxidant, and potent anti-bacterial activities, owing to the binding of functional groups from the plant extract to their surfaces (17).

In the present study, the *in vitro* efficacy of sumac (*R. coriaria*) was investigated against two leading causative agents of the Old World and the New World cutaneous leishmaniasis, *L. tropica* and *L. mexicana*, respectively. It was shown that all extracts of *R. coriaria* were effective against these *Leishmania* species in relatively higher doses, within 144.53 µg/mL and 578.13 µg/mL, compared to meglumine antimoniate (25 µg/mL). An interesting finding was that higher sumac doses were required to eliminate *L. tropica* compared with *L. mexicana* in this *in vitro* assessment. In other words, *R. coriaria* extracts were totally effective at half doses against *L. mexicana* compared with *L. tropica*. This study showed that the aqueous alcohol extract was effective at lower doses (289.06 µg/mL and 144.53 µg/mL for *L. tropica* and *L. mexicana*, respectively) compared with the other extracts. The fact that this effect continued at 48 h, along with the 24 h mark, was considered important in terms of the continuity and stability of the effect. These findings are particularly encouraging for the potential development of sumac-based treatment options for leishmaniasis. The sustained efficacy of the aqueous alcohol extract makes it a promising candidate for further investigation, potentially leading to more effective and practical treatment options.

In this study, different extracts of sumac (alcohol, aqueous-alcohol, infusion, acetone) were found to be effective against *L. tropica* promastigotes, the primary target of the study, to a degree comparable to the reference drug glucantime. In a further comparison, it was determined that the aqueous-alcohol extract of sumac, which was found to be the most effective, was much more potent against *L. mexicana* than *L. tropica*, eradicating *L. mexicana* promastigotes even when administered at half the dose. It is believed that future studies on the anti-leishmanial effects of sumac may be beneficial not only for the treatment of leishmaniasis in the Old World but also in the New World. The study's findings suggest that sumac-based treatments could hold promise for combating leishmaniasis not only in regions where *L. tropica* is prevalent but also in areas affected by *L. mexicana*. This has significant implications for developing more broadly effective treatments for this global health concern.

In conclusion, the aqueous alcohol extract of sumac was found to be at least as effective as meglumine antimoniate against *L. tropica* promastigotes under *in vitro* conditions. The most important limitation of this study is that the extracts were investigated only under *in vitro* conditions. The next step involves investigating the active compounds within the extract that could serve as potential drug candidates and testing them using *in vivo* models. Obtaining successful results in this stage would strengthen the possibility of a new drug option for this common neglected tropical disease, leishmaniasis.

Ethics Committee Approval: The study did not use human or animal material and experiments were conducted with parasite strains preserved in liquid nitrogen. Therefore, ethics committee approval is not required.
Peer Review: Externally peer-reviewed.
Author Contributions: Conception/Design of Study – E.M., Y.O., H.B., C.D., A.K., O.K.; Data Acquisition – E.M., Y.O., H.B.; Data Analysis/Interpretation – C.D., A.K., O.K.; Drafting Manuscript – E.M.,

Y.O., H.B., C.D., A.K., O.K.; Critical Revision of Manuscript – C.D., A.K., O.K.; Final Approval and Accountability – C.D., A.K., O.K.

Conflict of Interest: The authors have no conflict of interest to declare.

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