

## Syrian sumac (*Rhus coriaria* L.)—An effective medicinal plant against multidrug resistant uropathogenic *Escherichia coli*

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### ABSTRACT

Urinary tract infections (UTIs) are a global concern causing annual health and economic burdens, especially with the massive prevalence of resistant uropathogens. In recent decades, medicinal plants have gained increasing attention as a promising alternative to traditional antibiotics. In this study, the antibacterial activity of the hydroalcoholic sumac extract was tested on clinical Uropathogenic *Escherichia coli* (UPEC) isolates including multidrug resistance strains. In the well diffusion method, sumac was effective against all bacteria in a concentration-dependent manner with an inhibition diameter of 7–15 mm for UPEC and 17–23 mm for the reference strain. Minimum inhibitory concentration/minimum bactericidal concentration were of 3.125/3.125–6.25 mg/ml for UPEC and 0.0244/1.563 mg/ml for the reference strain. The extract reduced the hemagglutination of bacteria with human RBCs in all positive cases. Moreover, the extract inhibited the ability of UPEC to adhere to polystyrene surfaces at percentages of 79.1%–95.1%. However, the extract did not affect the morphology of bacteria except for one isolate where it resulted in cell elongation and formation of short filaments. Long exposure to the extract did not reduce the sensitivity of the bacteria to it. Accordingly, sumac represents a promising natural antibacterial agent for the development of based pharmaceuticals to treat and prevent UTIs caused by UPEC.

### INTRODUCTION

Urinary tract infections (UTIs) are classified among the most common bacterial infections, especially in women (Negus *et al.*, 2020). Annually, UTIs cause health, economic, and social burdens worldwide. With the continuous emergence of antibiotic resistance among uropathogens and the high rate of recurrence, controlling these infections becomes more challenging and the choices of antibiotherapy become less (Lodhia *et al.*, 2020; Negus *et al.*, 2020). Uropathogenic *Escherichia coli* (UPEC) is the most predominant cause of UTIs; it accounts for up to 80% of uncomplicated UTIs, 95% of community-acquired infections, and half of the infections acquired in hospitals (Kot, 2019). UPEC have developed a number of smart strategies that enable them to survive and colonize under the conditions of the urinary tract,

especially the constant flow of urine. These strategies are achieved by a variety of virulence factors such as fimbrial and nonfimbrial adhesins, curli, Lipopolysaccharides (LPS), surface vesicles, polysaccharide capsules, flagella, secreted toxins, two-component signaling systems, and the iron acquisition system (Terlizzi *et al.*, 2017).

Recently, multidrug resistance (MDR) has noticeably increased among UPEC because of the frequent and uncontrolled use of antibiotics, which resulted in a lack of treatment and prophylaxis choices (Chaudhary *et al.*, 2021). UPEC resistance to a wide range of antibiotics has already been reported worldwide (Terlizzi *et al.*, 2017). This resistance has led to complexity and high cost of treatment as well as prolonged hospitalization (Kot, 2019). Hence, antibiotic resistance in UPEC represents a heavy burden on individuals and governments, demonstrating the urgent need to develop alternative and effective approaches to counteract these highly prevalent infections. Indeed, several approaches are being worked on in this regard, such as vaccines, nanoparticles, probiotics, mannositides and galactosides, bacteriophages, and

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phytochemicals (Terlizzi *et al.*, 2017; Zalewska-Piątek and Piątek, 2019).

From time immemorial, humans have been using plants as a natural source of therapeutic compounds and traditional medicine became a rich reference for developing medicines to treat many health conditions. Recently, medicinal plants have been intensively studied as they represent a low-cost, effective, and ecofriendly source of medicinal compounds. This attention to medicinal plants has significantly increased in microbiology as tremendous efficiency of many plants was proved against a wide range of pathogens (Khameneh *et al.*, 2019; Shaheen *et al.*, 2019; Zalewska-Piątek and Piątek, 2019).

Syrian sumac is a worldwide consumed plant, especially in the Mediterranean region (Dziki *et al.*, 2021; Sakhr and El Khatib, 2020; Shabbir, 2012). The scientific name of sumac is *Rhus coriaria* Linn. (family Anacardiaceae) (Ravindran *et al.*, 2012). The common name “Syrian sumac” or “sumac” is mainly used to refer to the fruit of the plant *R. coriaria*, and it is believed to have an Arabic origin meaning dark red (Sakhr and El Khatib, 2020). Sumac is well known for its great nutritional and therapeutic properties and has been used in traditional medicine in Persia, Turkey, and the Mediterranean countries (Reidel *et al.*, 2017; Shabbir, 2012) where it grows abundantly in the form of small trees with a length of 1 to 3 m, giving small clustered fruits with a dark red color (Shabbir, 2012; Tohma *et al.*, 2019). These fruits are usually collected and dried well to use as a condiment or souring agent in various dishes (Farag *et al.*, 2018). In addition to its culinary use, sumac is increasingly gaining importance in the pharmaceutical and cosmetic industries (Sakhr and El Khatib, 2020). From a traditional perspective, sumac has been used to treat a variety of health conditions, such as liver diseases, diarrhea, ulcers, strokes, hemorrhoids, hemorrhage, animal bites, dysentery, diuresis, hematemesis, hemoptysis, ophthalmia, conjunctivitis, leucorrhea, sore throat, wounds, and high blood cholesterol, glucose, and uric acid levels, in addition to its use as a stomach tonic, abortifacient, and antimicrobial agent (Dziki *et al.*, 2021; Farag *et al.*, 2018; Shabbir, 2012). Due to its medical importance, researchers have paid great attention to this plant and indeed its effectiveness in treating and preventing many diseases has been proven. In several studies, sumac has been shown to exhibit antibacterial, antifungal, and antioxidant properties (Dziki *et al.*, 2021). Furthermore, sumac has been shown to reduce blood sugar (Shidfar *et al.*, 2014) and lipids (Akbari-Fakhrabadi *et al.*, 2018), in addition to its analgesic (Mohammadi *et al.*, 2016), anti-inflammatory, antihypertensive, and anticancer effect (Farag *et al.*, 2018). The benefits of sumac extends as far as protecting the liver (Pourahmad *et al.*, 2010) and cardiovascular system (Beretta *et al.*, 2009).

From the phytochemical point of view, sumac mainly contains hydrolysable tannins, polyphenols, flavonoids, anthocyanins, isoflavonoids, terpenoids, monoterpenes, diterpenes, organic acids, fatty acids, amino acids, vitamins, minerals, xylose, glucose, and essential oils (Ardalani *et al.*, 2016; Elagbar *et al.*, 2020; Farag *et al.*, 2018).

With regard to confronting bacterial pathogens, sumac has been shown to be a very effective antibacterial agent against

a wide range of Gram-negative and Gram-positive bacteria, including MDR strains (Akrai and Abdullrahman, 2013; Gabr and Alghadir, 2019; Mahdavi, 2018). To the authors’ knowledge, at the time of writing this article, we have not found any study that investigates the antibacterial activity of *R. coriaria* against UPEC. Therefore, we aimed to test the ability of this great plant to confront MDR UPEC.

## MATERIALS AND METHODS

### Bacteria, media, and growth conditions

This research was performed on eight clinical UPEC isolates. The reference strain *E. coli* ATCC 25922 was used as a quality control strain. All bacteria were provided by the Laboratory of Microbiology and Virology of the Peoples’ Friendship University of Russia in Moscow. The media used to grow bacteria consisted of brain heart infusion broth (BHIB) (HIMEDIA®, Ref. 173-500G) and Mueller–Hinton agar (MHA) (HIMEDIA®, Ref. 173-500G). For culturing bacteria, the following procedures were carried out, if not stated otherwise. Overnight cultures were prepared by growing bacteria in BHIB for 16 to 18 hours at 37°C in aerobic conditions. Bacterial inoculums were prepared by taking 1 ml of overnight cultures, centrifuging for 10 minutes at 3,000 rpm (in Eppendorf Centrifuge 5415 R), washing the centrifugate twice with phosphate buffer saline (PBS), and resuspending in physiological water (0.9% NaCl). The density of inoculums was adjusted photometrically to that of 0.5 McFarland standard so that they contained approximately  $1.5 \times 10^8$  colony forming units (CFUs)/ml. For antibiotic susceptibility tests, Petri dishes (90 mm) with 4 mm of MHA were used.

### Antibiotic susceptibility profile (antibiogram)

The Bauer–Kirby disk diffusion assay (Bauer *et al.*, 1966) was performed to obtain the antibiograms of the bacterial strains against eight antibiotics (HIMEDIA®): ampicillin (AMP), 25 µg/disc; ceftriaxone (CTR), 30 µg/disc; ciprofloxacin (CIP), 30 µg/disc; trimethoprim (TR), 30 µg/disc; ceftazidime/clavulanic acid (CAC), 30/10 µg/disc; ceftazidime (CAZ), 30 µg/disc; imipenem (IPM), 10 µg/disc; and tetracyclines (TE), 30 µg/disc. The procedure was performed in accordance with CLSI (2021) guidelines. Briefly, 100 µl of fresh bacterial inoculums (prepared as previously described) was spread on MHA plates and allowed to dry for 5 minutes. After that, antibiotic discs were placed onto the agar surface and the plates were incubated for 18 hours at 37°C. After incubation, diameters of growth-free zones were measured and recorded in mm. Bacterial sensitivity to antibiotics was interpreted in accordance with CLSI (2021) interpretative values.

### Multiple antibiotic resistance (MAR) Index and MDR identifying

The MAR index for each bacterial strain was calculated by dividing the number of antibiotics to which the bacterium is resistant by the total number of tested antibiotics (Ayandele *et al.*, 2020). Nonsusceptibility of bacteria to at least one agent in three or more antimicrobial categories has been defined as MDR (Basak *et al.*, 2016). Accordingly, MDR bacteria within the tested strains were further identified.

## Plant material and extraction

Sumac fruits were purchased from a local market in Tartous, Syria, in sun-dried, ground form. The hydroalcoholic extract of sumac was prepared by the extraction at room temperature method (Kothari *et al.*, 2012) with some modifications. Briefly, 80% ethanol was used as a solvent with a sample-to-solvent ratio of 1/10 (w/v). Fifty grams of ground sumac was placed in a 1,000 ml flask with the addition of 500 ml of 80% ethanol. The flask was then stoppered and covered with aluminum foil to prevent any evaporation and placed on a shaker (300 rpm) at room temperature (22°C) for 24 hours. Afterward, vacuum filtration was carried out to filter the mixture using Whatman filter paper № 1. Filtration was repeated three times. The filtrate was then concentrated using a rotary evaporator (IKA Werke, Staufen, Germany) at 40°C in a previously weighed flask. The yield of extraction was calculated as the percentage of the initial sumac mass. The concentrated crude extract was stored in the dark at 4°C until use.

## Preparation of working solution

A stock solution of the sumac crude extract was made in a concentration of 200 mg/ml in dimethyl sulfoxide (DMSO) (VWR International LLC, USA) (10% v/v in dH<sub>2</sub>O), sterilized via passing through a Millipore filter (0.22 µm), and stored in the dark at 4°C. The solution was always refiltered prior to each experiment.

## Antibacterial screening of sumac extract against UPEC

### Well diffusion method

To assess the antibacterial activity of the sumac extract against UPEC, the agar well diffusion method was carried out as described by Balouiri *et al.* (2016). Briefly, after seeding MHA plates with 100 µl of fresh bacterial inoculums, wells were aseptically made in the agar by a 6 mm cork borer, followed by loading the wells with 45 µl of the sumac extract in three concentrations: 50, 100, and 200 mg/ml. DMSO (10%) was included as the negative control. The plates were then incubated for 24 hours at 37°C, after which the diameters of growth-free zones were measured and recorded in mm.

### Quantitative antibacterial assay by minimum inhibitory concentrations (MICs) and minimum bactericidal concentrations (MBCs)

The broth microdilution method was used to determine the MICs of the sumac extract as previously described (Wiegand *et al.*, 2008). In brief, the assay was performed in sterile U-bottomed 96-well microplates. Serial two-fold dilutions were made from the stock solution of the sumac extract in BHIB. Then, 50 µl of each dilution and 50 µl of fresh bacterial inoculums were added to the respective wells. The final density of bacteria in all wells was approximately  $5 \times 10^5$  CFUs/ml, and the final concentrations of the extract ranged from 100 to 0.0031 mg/ml. DMSO (10%) was used as a negative control. Wells with all used solutions, except bacteria, were included to check sterility. Microplates were then incubated for 16–20 hours at 37°C. After incubation, the lowest concentration of extract that inhibited the visible growth of bacteria was considered as MIC. To determine MBCs, a loopful of each clear well was streaked onto an MHA plate and incubated for

18 hours at 37°C (Lara *et al.*, 2016). The lowest concentration that resulted in no bacterial growth on the agar plates was considered as MBC.

### Yeast agglutination (YA)

The sumac extract in subinhibitory concentration was tested to observe any effect on the ability of bacteria to agglutinate with yeast cells (*Saccharomyces cerevisiae*). The previously described slide method (Stærk *et al.*, 2016) was performed with some modifications. Standardized concentrations (OD<sub>492</sub> = 0.05) of overnight cultures were added to BHIB containing the sumac extract in a final concentration that equals MIC/2 and incubated at 37°C for 24 hours. Control cultures were included with the substitution of the extract by 10% DMSO. Following the incubation period, cultures were centrifuged, washed twice, and resuspended in PBS. Agglutination tests were performed on sterile glass slides at room temperature by mixing 20 µl of bacterial suspension with an equal volume of yeast suspension (1% w/v in PBS). The visible appearance of aggregates was observed within 10 minutes and evaluated as follows: – (no agglutination), + (weak), ++ (moderate), or +++ (strong). To assess the effect of mannose on agglutination, the same procedure was performed with the addition of 20 µl of D-mannose (1% in PBS). Mannose-resistant (MR) indicates the same degree of agglutination with and without mannose, whereas mannose-sensitive (MS) indicates that the agglutination was completely inhibited or significantly reduced in the presence of mannose. Further, agglutination was confirmed by light microscopy at 100×.

### Hemagglutination (HA)

The hHA assay was performed by the slide method previously described (Evans *et al.*, 1980) with some modifications. Fresh human RBCs (B+) from a healthy man were obtained from the university clinic. After washing twice, a 5% suspension was made in PBS. Bacteria were incubated with and without sumac exactly as described for YA. On sterile glass slides, equal volumes of bacterial suspensions and RBCs were mixed, in the presence and absence of D-mannose. HA was observed within 10 minutes and evaluated as described for YA. Aggregates were further observed using light microscopy at 100×.

### Adhesion to polystyrene

The capacity of UPEC to adhere to polystyrene surfaces was investigated in the presence and absence of sumac. First, bacteria were incubated with the sumac extract (at MIC/2) or DMSO (control), as described for the YA test. After incubation, 2 ml of each culture was poured onto polystyrene Petri dishes (4 cm) and allowed to stand for 4 hours at room temperature. Afterward, dishes were washed from planktonic bacteria with sterile distilled water and adhered bacteria were stained with 2 ml of 1% crystal violet for 10 minutes. The dishes were rinsed with sterile distilled water to remove the excess dye and then air-dried. Adhesion of bacteria to Petri surfaces was observed by light microscopy at 1,000×. In order to evaluate the difference in adhesion between treated and nontreated bacteria, adhered cells were counted in 10 random fields of view, the mean was calculated, and the *p* value was further identified for 3 trials. Inhibition of adhesion was expressed as a percentage of the control groups.



### Morphology

Light microscopy was used to investigate any morphological changes in the general shape and dimension of UPEC after exposure to the sumac extract. Standardized concentrations ( $OD_{492} = 0.05$ ) of overnight cultures were incubated with the extract at MIC/2 in BHIB for 24 hours at 37°C, after which cultures were washed twice and resuspended in PBS. Finally, bacteria were Gram-stained and observed under a light microscope at 1,000 $\times$ . In each sample, 100 random cells were observed. Images and measurements were obtained by Levenhuk M300 Base Digital Camera and Levenhuk ToupView (3.7.6273) software. Control cultures consisted of bacteria incubated with 10% DMSO.

### Changes in antibiogram and susceptibility to sumac after long exposure to the extract

To investigate if long exposure to sumac can affect bacterial susceptibility to antibiotics or to the extract, the following assay was performed. In a sterile U-bottomed 96-well microplate, 100  $\mu$ l of the sumac extract at MIC was added to 100  $\mu$ l of BHIB, giving a final concentration of MIC/2. Afterward, wells in the A-row were inoculated with 10  $\mu$ l of fresh bacterial inoculums and the microplate was incubated at 37°C. The next day, wells in the A-row were homogenized and 10  $\mu$ l of each was introduced to the corresponding well in the B-row and incubated again and so forth until the fourth day. At this point, 10  $\mu$ l of the last generation was added to sumac-free BHIB and incubated overnight. Subsequently, antibiograms and MICs were determined as aforementioned. As a negative control, the same procedure was simultaneously performed with 10% DMSO instead of extract.

### Statistical analysis

All experiments were performed separately in triplicate. Excel 2019 was used to analyze data and to calculate means and standard deviations (SD). Statistical significance was evaluated by Student's *t*-test with  $p < 0.05$  reflecting a statistically significant difference.

## RESULTS AND DISCUSSION

### Extraction

The final sumac crude extract was in the form of a dark red semisolid mass. Extraction yield comprised 42% of the initial raw mass. In general, extraction yield differs according to the used extraction method, type of solvent, and duration of extraction and drying, among other factors (Kothari *et al.*, 2012).

### Antibiotic susceptibility profile (antibiogram) before and after long exposure to sumac extract

The prevalence of antibiotic resistance among UPEC is becoming a worldwide threat that complicates UTIs treatment and prophylaxis (Ballesteros-Monreal *et al.*, 2020). The susceptibility of UPEC clinical isolates to eight antibiotics was determined and interpreted according to CLSI (2021). The results are shown in Table 1. In a total of eight isolates, resistance was highly observed to AMP (five isolates), whereas the most sensitivity was to IPM (seven isolates) followed by CIP (six

isolates). High AMP resistance among UPEC has been reported in many studies (Greer *et al.*, 2008; Gupta *et al.*, 1999; Hart *et al.*, 2001). This resistance is mainly due to  $\beta$ -lactamase production; thus, the combination of AMP with  $\beta$ -lactamase inhibitors became an alternative to overcome resistance (Sáez-Llorens and McCracken, 2006). IPM is still one of the best treatment options for UTIs, especially those caused by Extended-spectrum beta-lactamases (ESBL)-producing strains (Kot, 2019; Terlizzi *et al.*, 2017). TE, CAC, CAZ, and TR were effective against five isolates. However, none of the tested antibiotics was effective against all isolates.

Furthermore, the capacity of the sumac extract to modulate bacterial susceptibility to antibiotics was investigated. The results showed no significant changes had been caused by long exposure to the sumac extract ( $p > 0.05$ ) (Table 1). Control samples, which have been incubated with DMSO, showed the same susceptibility as for nontreated normal bacteria ( $p > 0.05$ ) (data not shown). Interestingly, Samoilova *et al.* (2014) reported that plant extracts modulate *E. coli* responses to antibiotics. The modulation effect, whether enhancing or reducing susceptibility, depended on the antibiotic with which the bacteria were treated as the plants' extracts exhibited a protective effect for bacteria from CIP and AMP, while the bactericidal effect of kanamycin was enhanced. The authors suggested that these modulation effects are more likely due to some properties of polyphenols such as antioxidant, iron-chelating, or prooxidant activity. Here, we did not observe any change in susceptibility to the tested antibiotics after 4 d of exposure to the sumac extract. We suppose that many factors may play a role in the modulation effect caused by plant extracts, such as duration of exposure, phytochemical content of the extract, extract concentration, and type of tested bacteria and antibiotics, among other possibilities.

### MAR index and MDR identifying

The MAR index is a simple and cost-effective indicator of the level of multiresistance in bacteria, and it also presents an idea about the source of isolate in terms of frequency of using antibiotics (Ayandele *et al.*, 2020). MAR values greater than 0.2 indicate MAR bacteria which exist in a high-risk contaminated source where antibiotics are frequently used (Adenaike *et al.*, 2016; Osundiya *et al.*, 2013). Here, we determined the MAR index of eight UPEC isolates (Table 2). Four isolates were identified as MAR, one of them exhibited resistance to all tested antibiotics (MAR index = 1), and three showed a MAR index greater than 0.2 (0.75, 0.625, and 0.375). However, three isolates were sensitive to all tested antibiotics (MAR index = 0). MAR *E. coli* (Adenaike *et al.*, 2016; Ayandele *et al.*, 2020; Titilawo *et al.*, 2015) and MAR UPEC (Baldiris-Avila *et al.*, 2020; De Souza *et al.*, 2019) have been already reported. Generally, the high prevalence of MAR bacteria requires more clinical investigations and strong control of antibiotic use since misuse of antibiotics causes bacteria to accumulate resistance genes and increase multidrug efflux pumps and eventually become MDR (Nikaido, 2009). All MAR strains in this study have been shown to be also MDR which accounts for 50% of the total number of tested isolates. This correlates with recent studies (Hassuna *et al.*, 2020;

**Table 1.** Antibigram of *E. coli* strains. A: nontreated. B: after 4 days of incubation with the sumac extract.

Strains	TE <sup>a</sup>		CAC		CIP		CAZ	
	A	B	A	B	A	B	A	B
UPEC 1	22 ± 0.0 <sup>(S)</sup> <sup>b</sup>	22 ± 0.7 <sup>(S)</sup>	22 ± 0.9 <sup>(S)</sup>	23 ± 0.5 <sup>(S)</sup>	30 ± 0.3 <sup>(S)</sup>	29 ± 1.3 <sup>(S)</sup>	24 ± 0.0 <sup>(S)</sup>	24 ± 0.2 <sup>(S)</sup>
UPEC 2	25 ± 0.7 <sup>(S)</sup>	26 ± 0.9 <sup>(S)</sup>	22 ± 0.5 <sup>(S)</sup>	22 ± 1.2 <sup>(S)</sup>	32 ± 0.2 <sup>(S)</sup>	31 ± 1.4 <sup>(S)</sup>	24 ± 0.2 <sup>(S)</sup>	23 ± 1.0 <sup>(S)</sup>
UPEC 3	24 ± 0.3 <sup>(S)</sup>	25 ± 1.0 <sup>(S)</sup>	0 ± 0.0 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>	15 ± 0.7 <sup>(R)</sup>	15 ± 0.6 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>
UPEC 4	10 ± 1.5 <sup>(R)</sup>	11 ± 0.8 <sup>(R)</sup>	21 ± 1.3 <sup>(S)</sup>	22 ± 1.1 <sup>(S)</sup>	26 ± 0.3 <sup>(S)</sup>	27 ± 1.1 <sup>(S)</sup>	25 ± 0.3 <sup>(S)</sup>	25 ± 0.4 <sup>(S)</sup>
UPEC 5	10 ± 0.0 <sup>(R)</sup>	10 ± 0.4 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>	32 ± 0.8 <sup>(S)</sup>	33 ± 0.4 <sup>(S)</sup>	0 ± 0.0 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>
UPEC 6	21 ± 0.6 <sup>(S)</sup>	21 ± 0.0 <sup>(S)</sup>	18 ± 0.3 <sup>(S)</sup>	18 ± 1.3 <sup>(S)</sup>	31 ± 0.5 <sup>(S)</sup>	31 ± 0.0 <sup>(S)</sup>	19 ± 0.7 <sup>(S)</sup>	19 ± 0.1 <sup>(S)</sup>
UPEC 7	23 ± 1.9 <sup>(S)</sup>	22 ± 0.6 <sup>(S)</sup>	22 ± 0.1 <sup>(S)</sup>	23 ± 1.0 <sup>(S)</sup>	27 ± 1.5 <sup>(S)</sup>	25 ± 0.9 <sup>(S)</sup>	24 ± 0.1 <sup>(S)</sup>	24 ± 0.6 <sup>(S)</sup>
UPEC 8	11 ± 0.9 <sup>(R)</sup>	11 ± 1.0 <sup>(R)</sup>	12 ± 0.0 <sup>(R)</sup>	12 ± 0.0 <sup>(R)</sup>	11 ± 0.4 <sup>(R)</sup>	10 ± 0.8 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>
ATCC 25922	24 ± 0.5 <sup>(S)</sup>	25 ± 0.7 <sup>(S)</sup>	30 ± 0.2 <sup>(S)</sup>	30 ± 0.6 <sup>(S)</sup>	41 ± 0.2 <sup>(S)</sup>	40 ± 1.2 <sup>(S)</sup>	29 ± 0.5 <sup>(S)</sup>	28 ± 0.7 <sup>(S)</sup>

<sup>a</sup> TE: tetracyclines, CAC: ceftazidime/clavulanic acid, CAZ: ceftazidime, IPM: imipenem, CTR: ceftriaxone, TR: trimethoprim, and AMP: ampicillin.

<sup>b</sup> Diameter of inhibition zone in mm, presented as mean of three trials ± SD (sensitivity: R = resistant, I = intermediate, and S = sensitive).

**Table 1. (Continued)**

Strains	IPM		CTR		TR		AMP	
	A	B	A	B	A	B	A	B
UPEC 1	25 ± 1.5 <sup>(S)</sup>	26 ± 0.7 <sup>(S)</sup>	26 ± 0.9 <sup>(S)</sup>	27 ± 1.2 <sup>(S)</sup>	26 ± 0.7 <sup>(S)</sup>	27 ± 1.3 <sup>(S)</sup>	22 ± 0.0 <sup>(S)</sup>	22 ± 1.2 <sup>(S)</sup>
UPEC 2	28 ± 0.5 <sup>(S)</sup>	28 ± 0.5 <sup>(S)</sup>	26 ± 1.8 <sup>(S)</sup>	28 ± 0.9 <sup>(S)</sup>	30 ± 0.4 <sup>(S)</sup>	29 ± 0.9 <sup>(S)</sup>	22 ± 1.9 <sup>(S)</sup>	21 ± 0.3 <sup>(S)</sup>
UPEC 3	24 ± 0.9 <sup>(S)</sup>	24 ± 0.9 <sup>(S)</sup>	7 ± 0.9 <sup>(R)</sup>	7 ± 0.0 <sup>(R)</sup>	33 ± 0.2 <sup>(S)</sup>	33 ± 0.0 <sup>(S)</sup>	0 ± 0.0 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>
UPEC 4	28 ± 0.0 <sup>(S)</sup>	28 ± 0.8 <sup>(S)</sup>	30 ± 1.0 <sup>(S)</sup>	32 ± 1.4 <sup>(S)</sup>	0 ± 0.0 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>
UPEC 5	32 ± 0.9 <sup>(S)</sup>	31 ± 0.5 <sup>(S)</sup>	0 ± 0.0 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>
UPEC 6	28 ± 1.1 <sup>(S)</sup>	28 ± 0.2 <sup>(S)</sup>	25 ± 0.7 <sup>(S)</sup>	25 ± 0.0 <sup>(S)</sup>	28 ± 0.3 <sup>(S)</sup>	28 ± 0.4 <sup>(S)</sup>	19 ± 0.4 <sup>(S)</sup>	20 ± 0.9 <sup>(S)</sup>
UPEC 7	26 ± 0.8 <sup>(S)</sup>	26 ± 0.0 <sup>(S)</sup>	27 ± 0.9 <sup>(S)</sup>	27 ± 0.7 <sup>(S)</sup>	31 ± 1.2 <sup>(S)</sup>	31 ± 0.3 <sup>(S)</sup>	0 ± 0.0 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>
UPEC 8	13 ± 0.4 <sup>(R)</sup>	14 ± 0.9 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>	0 ± 0.0 <sup>(R)</sup>
ATCC 25922	32 ± 0.4 <sup>(S)</sup>	32 ± 0.1 <sup>(S)</sup>	32 ± 0.2 <sup>(S)</sup>	32 ± 1.1 <sup>(S)</sup>	36 ± 0.3 <sup>(S)</sup>	36 ± 0.9 <sup>(S)</sup>	38 ± 0.5 <sup>(S)</sup>	37 ± 1.1 <sup>(S)</sup>

**Table 2.** MAR index and MDR identifying.

Strains	Number of antibiotics			MDR
	Resistant	Tested	MAR index	
UPEC 1	0	8	0	–
UPEC 2	0	8	0	–
UPEC 3	5	8	0.625	+
UPEC 4	3	8	0.375	+
UPEC 5	6	8	0.75	+
UPEC 6	0	8	0	–
UPEC 7	1	8	0.125	–
UPEC 8	8	8	1	+
ATCC 25922	0	8	0	–

**Table 3.** Well diffusion results for sumac extract against *E. coli*.

Strains	Extract (mg/ml)		
	50	100	200
UPEC 1	8 ± 0.7 <sup>a</sup>	12 ± 0.1	14 ± 0.5
UPEC 2	9 ± 0.9	12 ± 0.0	14 ± 0.3
UPEC 3	9 ± 1.1	12 ± 0.4	15 ± 0.0
UPEC 4	8 ± 0.5	13 ± 0.8	14 ± 0.0
UPEC 5	8 ± 0.3	11 ± 0.1	15 ± 0.2
UPEC 6	8 ± 0.0	10 ± 0.0	14 ± 0.3
UPEC 7	7 ± 1.5	10 ± 0.2	13 ± 0.0
UPEC 8	8 ± 0.2	12 ± 0.1	14 ± 0.0
ATCC 25922	17 ± 0.0	19 ± 0.4	23 ± 0.2

<sup>a</sup> Diameter of inhibition zone in mm (mean of three trials) ± SD.

Vasudevan *et al.*, 2020; Zhong *et al.*, 2020) where MDR UPEC were identified at high rates.

### Well diffusion method

As a first screening, the antibacterial activity of the sumac extract was examined by the well diffusion method (Table 3, Fig. 1). All tested strains showed a considerable susceptibility to the extract in a concentration-dependent manner.

There was not a significant difference in susceptibility between UPEC isolates (7–15 mm), while *E. coli* ATCC 25922 showed significantly higher susceptibility (17–23 mm). These findings correlate with other studies where the antibacterial activity of the sumac hydroalcoholic (Fazeli *et al.*, 2007) and aqueous (Nasar-Abbas and Halkman, 2004; Vahid-Dastjerdi *et al.*, 2014) extracts was significant against several Gram-negative and Gram-positive

bacteria. Similarly, sumac essential oil was found to inhibit *Pseudomonas aeruginosa*, *E. coli*, *Staphylococcus aureus*, and *Bacillus subtilis* (Zhaleh *et al.*, 2018). Additionally, the sumac aqueous extract strongly inhibited the growth of a MDR *S. aureus* isolate, *in vitro* and *in vivo* (Akrayi and Abdullrahman, 2013). Interestingly, the sumac ethanolic extract has been shown to exhibit a synergistic effect with antimicrobial drugs (oxytetracycline HCl, penicillin G, cephalixin, sulfadimethoxine as sodium, and enrofloxacin) against MDR *P. aeruginosa* (Adwan *et al.*, 2010). In a similar manner, sumac has been reported to exert antibacterial activity against Gram-negative and Gram-positive strains, including *S. aureus*, *P. aeruginosa*, *S. aureus* Methicillin Resistant Staphylococcus Aureus (MRSA), and *Salmonella enterica* (Gabr and Alghadir, 2019; Mahdavi, 2018). Thus, our results support the reported antibacterial activity of sumac. This activity could be mainly attributed to sumac rich content of phytochemicals, especially phenolic compounds (Ardalani *et al.*, 2016; Elagbar *et al.*, 2020; Farag *et al.*, 2018) which are known to interact with bacterial bioprocesses (Mandal *et al.*, 2017; Takó *et al.*, 2020).

MICs and MBCs

A quantitative antibacterial assay of the sumac extract was performed by determining MICs and MBCs (Table 4). The extract showed a MIC of 3.125 mg/ml against all tested UPEC isolates whereas the reference strain required a far lower concentration (0.0244 mg/ml) to inhibit visible bacterial growth. The MICs of seven isolates have been shown to be also MBCs, whereas one isolate and ATCC 25922 had an MBC of 6.25 and 1.563 mg/ml, respectively. Similar low MICs of sumac were reported against *E. coli* strains: 2 mg/ml for hydroalcoholic extract (Fazeli *et al.*, 2007), 3 mg/ml for hydrodistilled essential oil (Elagbar *et al.*, 2020), and 6–6.3 mg/ml for aqueous extract (Nasar-Abbas and Halkman, 2004).

Bacteria are smart organisms that surprisingly evolve various mechanisms to survive in unsuitable environments and adapt to antibacterials. This fact can be seen obviously in the rapid prevalence of antibiotic resistance. Interestingly, bacteria are shown to develop less resistance to phytochemicals (Shaheen *et al.*, 2019). To inspect this, adaptation of bacteria to the sumac extract after long exposure to it was investigated. The results showed no alteration in susceptibility to the extract as the MICs were the same as for normal nontreated bacteria (Table 4). On the contrary, a study has shown an increase in MIC for the sumac aqueous extract after three3 and seven7 days of exposure to it (Nasar-Abbas and Halkman, 2004). Moreover, loss of antibacterial activity with prolonged incubation was also reported for other herbs (Shelef, 1984), which raises an important question of whether the resistance against phytochemicals could also emerge and shrink the efficacy of medicinal plants against bacterial pathogens.

YA and HA

Adhesion to host cells is a critical stage for bacteria to colonize and form biofilms (Nizet *et al.*, 2015). Bacterial adhesion is mainly mediated by lectins that bind to specific sugar moieties on other cell types (Mrázková *et al.*, 2019). Agglutination is a simple and cost-effective test to investigate adhesive properties

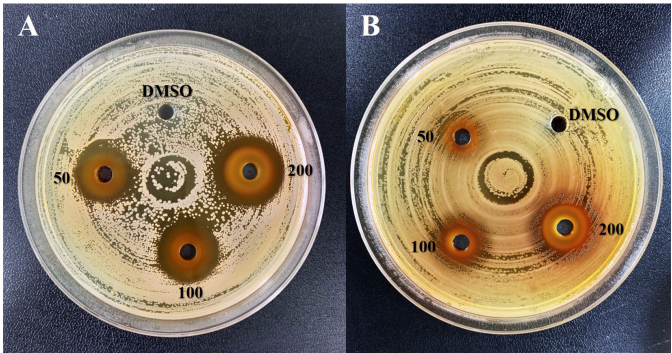


Figure 1. Well diffusion method: inhibition zones of sumac extract at 50, 100, and 200 mg/ml. A: *E. coli* ATCC 25922. B: UPEC3. DMSO: negative control.

Table 4. MICs and MBCs of the sumac extract. A: nontreated bacteria. B: bacteria after long exposure to sumac.

Strains	MIC (mg/ml)		MBC (mg/ml)
	A	B	A
UPEC 1	3.125 ± 0.0	3.125 ± 0.0	6.25 ± 0.0
UPEC 2	3.125 ± 0.0	3.125 ± 0.0	3.125 ± 0.0
UPEC 3	3.125 ± 0.0	3.125 ± 0.0	3.125 ± 0.0
UPEC 4	3.125 ± 0.0	3.125 ± 0.0	3.125 ± 0.0
UPEC 5	3.125 ± 0.0	3.125 ± 0.0	3.125 ± 0.0
UPEC 6	3.125 ± 0.0	3.125 ± 0.0	3.125 ± 0.0
UPEC 7	3.125 ± 0.0	3.125 ± 0.0	3.125 ± 0.0
UPEC 8	3.125 ± 0.0	3.125 ± 0.0	3.125 ± 0.0
ATCC 25922	0.0244 ± 0.0	0.0244 ± 0.0	1.563 ± 0.0

of bacteria. Here, adhesion of UPEC to yeast cells (*S. cerevisiae*) and human RBCs was investigated after exposure to the sumac extract (Table 5). The presence of aggregates in both assays was confirmed under a light microscope (Fig. 2).

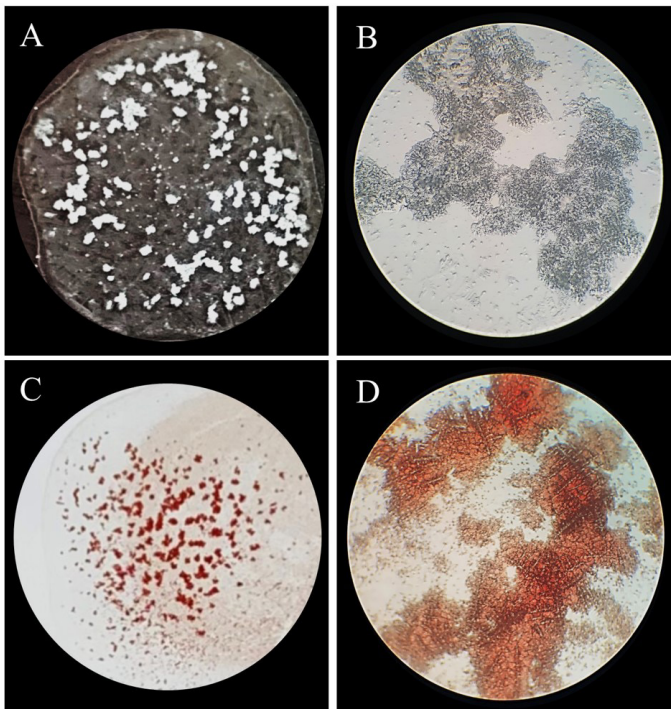
Out of eight isolates, seven were able to agglutinate with yeast cells in an MR manner; five of them showed strong agglutination whereas the other two were moderate. The sumac extract did not show any effect on the YA pattern of any isolate. Type 1 fimbriae (T1F) are widely expressed MS fimbriae in *E. coli*, and they are known to mediate binding of UPEC to mannoseylated proteins (uropelkins) on the bladder epithelium (Kisiela *et al.*, 2013; Stærk *et al.*, 2016). T1F are encoded by the *Fim* operon which is a constitutive gene cluster located on the chromosome. The expression of this operon is a Phase variable which enables the bacterial cell to change between the Phase-ON (fimbriated cells) and the Phase-OFF (nonfimbriated cells) in response to environmental signals within the urinary tract (Terlizzi *et al.*, 2017). Tamm–Horsfall proteins are mannoseylated glycoproteins that normally exist in human urine as a part of the innate immune response. These proteins can bind to the TIF of UPEC and thus decrease their ability to bind to uropelkins (Scharf *et al.*, 2019). From the aforementioned facts, it could be assumed that the Mannose-resistant yeast agglutination (MRYA) we observed



**Table 5.** Agglutination patterns of *E. coli* with yeast (YA) and human RBCs (HA).

	Strains	UPEC 1	UPEC 2	UPEC 3	UPEC 4	UPEC 5	UPEC 6	UPEC 7	UPEC 8	ATCC 25922
YA	Control	++ MR*	—	++ MR	+++ MR	+++ MR	+++ MR	+++ MR	+++ MR	—
	Extract	++ MR	—	++ MR	+++ MR	+++ MR	+++ MR	+++ MR	+++ MR	—
HA	Control	—	—	—	++ MS	++ MS	++ MS	+++ MR	+++ MR	—
	Extract	—	—	—	—	—	—	+ MR	+ MR	—

\*—: no agglutination, +: weak, ++: moderate, +++: strong, MR: mannose-resistant, and MS: mannose-sensitive.



**Figure 2.** Strong agglutination of UPEC 8 with yeast cells (A, B) and human RBCs (C, D). Aggregates on slides (A, C) and under a light microscope (100×) (B, D).

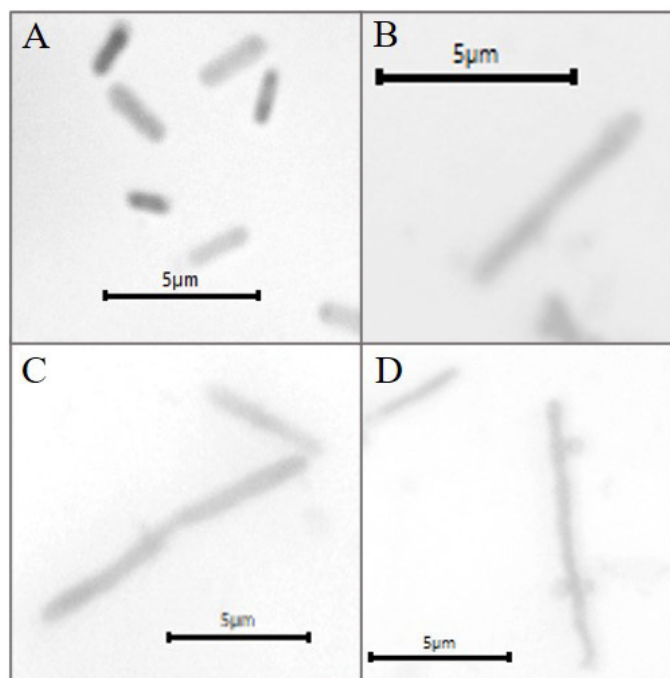
in UPEC indicates a switched-off expression of T1F which is probably a defense response against Tamm-Horsfall proteins. A study conducted by [Greene \*et al.\* \(2015\)](#) supports this paradox by showing that when they are grown in human urine, expression and function of T1F in UPEC were inhibited and only restored by attachment to human bladder cells. Thus, it becomes predictable for planktonic UPEC in urine to lack effective T1F.

HA typing is commonly performed with human or animal RBCs to investigate hemagglutinating properties of bacterial cells ([Evans \*et al.\*, 1980](#)) which have been associated with the adhesive capacity to epithelial cells ([Alp \*et al.\*, 2010](#); [Hagberg \*et al.\*, 1981](#)). Here, five UPEC isolates were able to agglutinate with RBCs: three with a strong Mannose-resistant hemagglutination (MRHA) and two with a moderate MSHA. However, three isolates did not show any agglutination activity. The extract reduced HA in all positive cases by two degrees; i.e., strong HA became weak and moderate became negative. *Escherichia coli* have been reported to have various agglutination patterns with human RBCs depending on many factors such as culturing media and used blood group ([Hrv \*et al.\*, 2016](#); [Shareef \*et al.\*, 2010](#)). MRHA with

human RBCs is shown to be mediated mainly by P pili, one of the most common MR fimbriae in UPEC that mediate binding to the digalactoside epitope (Gal $\alpha$ -1,4-Gal $\beta$ ) of glycolipids on epithelial kidney cells and P-blood group erythrocytes. P pili are evolved in kidneys colonization by UPEC and highly associated with pyelonephritis ([Busch \*et al.\*, 2015](#); [Möller \*et al.\*, 1983](#)). However, optimizing growth conditions ([Mikcha \*et al.\*, 2004](#)) and selecting the appropriate blood group ([Hrv \*et al.\*, 2016](#)) are essential to evaluate the HA activity of bacteria. Here, we mainly aimed to investigate the effect of the extract on bacterial HA patterns. Hence, we conclude that the extract was able to reduce the HA for all agglutinating bacteria suggesting downregulation of the mediating fimbriae. Therefore, sumac could be suspected to have an inhibiting effect on the adhesion capacity of UPEC *in vivo*.

#### Adhesion on polystyrene

Bacterial adhesion is not confined to living tissues but also widely found on abiotic surfaces with the subsequent formation of biofilms ([Dunne, 2002](#)). Biofilms represent a worrisome global issue as they are more resistant to antibacterial agents and harder to eliminate. This issue is highly associated with medical implants such as ventilators, catheters, contact lenses, and heart valves, complicating treatment and causing chronic inflammation ([Simo, 2020](#)). In this study, we investigated the effect of the sumac extract on the adhesion capacity of UPEC to polystyrene. The results revealed that the sumac extract significantly inhibited ( $p < 0.05$ ) the adhesion of seven isolates at the following percentages: 95.1%, 94.3%, 92.1%, 91.8%, 85.4%, 82.7%, and 79.1%  $\pm$  0.4%–1.3%. Polystyrene surfaces are routinely used as *in vitro* platforms to investigate bacterial adhesion and biofilm formation ([Kirmusaoglu, 2019](#)). A correlation between bacterial adhesion to polystyrene and epithelial cells has been reported ([Ruiz \*et al.\*, 2011](#)). Moreover, the adhesion ability of bacteria to polystyrene is considered a problem of significance for plastic-based surgical material and medical implants ([Khatoon \*et al.\*, 2018](#)). Phytochemicals have been widely reported to exert antiadhesive and antibiofilm activity against UPEC ([Amalaradjou \*et al.\*, 2010](#); [Lagha \*et al.\*, 2019](#); [Packiavathy \*et al.\*, 2014](#); [Rodríguez-Pérez \*et al.\*, 2016](#)). In particular, sumac has been shown to inhibit *Streptococcus mutans* biofilm formation and suppress the acidogenicity of the formed biofilm ([Kacergius \*et al.\*, 2017](#)). This antibiofilm activity was mainly attributed to the presence of methyl gallate in the sumac methanolic extract. Similarly, sumac seems to protect against dental caries and plaque as its water extract inhibited five common oral bacteria (*Streptococcus* species and *Enterococcus faecalis*) and their ability to form biofilms ([Vahid-Dastjerdi \*et al.\*, 2014](#)). Here, we showed that sumac could be an effective antiadhesive agent against UPEC as it effectively decreased their ability to adhere to polystyrene. This inhibition is more likely to be due to modification of bacterial cell surface hydrophobicity which is a crucial determinant in



**Figure 3.** Morphological changes in UPEC 3 after incubation with the sumac extract. A: normal cells. B, C, and D: short filaments (5–10 µm). Magnification 1,000×.

bacterial adhesion to biotic and abiotic surfaces (Krasowska and Sigler, 2014). These findings are promising in confronting biofilm formation on medical devices as they could have applications in catheter surface coating or lock solution, which in turn will greatly contribute to preventing UTIs.

#### Morphological changes in UPEC after exposure to sumac extract

The capacity of the sumac extract to cause morphological changes in UPEC was investigated. For seven isolates, no differences were observed between the control and treated samples as they all contained rods of normal dimensions: length of 1–4 µm and diameter of 0.3–0.7 µm. On the contrary, a significant increase in length was observed in one isolate (UPEC 3) as the length of the control sample was of 1–3 µm, while 80% of treated cells were >4 µm and up to 8.4 µm (short filaments) (Fig. 3). SD for all the aforementioned values was of 0.4–1.3. Plant secondary metabolites have been shown to have different effects on bacterial cell morphology, probably depending on the tested bacteria and on the chemical nature of these compounds. For instance, in some studies, bacteria became visibly shorter after exposure to phytochemicals (Kurek *et al.*, 2010; Szakiel *et al.*, 2008), whereas in other cases the formation of filaments was highly induced by phytochemicals (Dorota *et al.*, 2013). Bacterial filamentation is an abnormal growth in which cells grow in long threadlike strands composed of nondividing elongated cells. This phenomenon has been suggested to be a result of several factors such as DNA damage, defects in cell division by which bacteria lose the ability to separate at the end of the division, unfavorable environment, or antibiotics treatment (Buijs *et al.*, 2008; Dorota *et al.*, 2013; Justice *et al.*, 2008). Here, we found that the sumac extract

highly caused the bacterial cells of one UPEC strain to become significantly longer and to form short filaments. This observation may indicate a stress condition to bacteria caused by the sumac extract or penetration of active phytochemicals into bacterial cells, damaging DNA or interacting with the replication process.

#### CONCLUSION

Sumac appears as a promising medicinal plant for developing antibacterial pharmaceuticals against MDR UPEC. This study represents a basis for a variety of further investigations including identifying active compounds responsible for the antibacterial properties, investigating *in vivo* cytotoxicity, and determining the precise mechanisms of action.

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#### LIST OF ABBREVIATIONS

UPEC: Uropathogenic *Escherichia coli*; UTIs: Urinary tract infections; MAR: Multiple antibiotic resistance; MDR: Multidrug resistance; YA: Yeast agglutination; HA: Hemagglutination; MS: Mannose-sensitive; MR: Mannose-resistant; T1F: Type 1 fimbriae.

#### CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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#### ETHICAL APPROVAL

This study does not involve experiments on animals or human subjects.

#### AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be authors as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

#### REFERENCES

- Adenaike O, Olonitola OS, Ameh, Whong CMZ. Multidrug resistance and multiple antibiotic resistance index of *Escherichia coli* strains isolated from retail smoked fish. J Nat Sci Res, 2016; 6:7–10.
- Adwan G, Abu-Shanab B, Adwan K. Antibacterial activities of some plant extracts alone and in combination with different antimicrobials against multidrug-resistant *Pseudomonas aeruginosa* strains. Asian Pac J Trop Med, 2010; 3:266–9; doi:10.1016/S1995-7645(10)60064-8.
- Akbari-Fakhrabadi M, Heshmati J, Sepidarkish M, Shidfar F. Effect of sumac (*Rhus Coriaria*) on blood lipids: a systematic review and meta-analysis.



Complement Ther Med, 2018; 40:8–12; doi:10.1016/j.ctim.2018.07.001.

Akrai HFS, Abdullrahman ZFA. Screening *in vitro* and *in vivo* the antibacterial activity of *Rhus Coriaria* extract against *S. aureus*. IJRRAS, 2013; 15:390–7.

Alp G, Aslim B, Suludere Z, Akca G. The role of hemagglutination and effect of exopolysaccharide production on bifidobacteria adhesion to Caco-2 cells *in vitro*. Microbiol Immunol, 2010; 54:658–65; doi:10.1111/j.1348-0421.2010.00227.x.

Amalaradjou MAR, Narayanan A, Baskaran SA, Venkitanarayanan K. Antibiofilm effect of trans-cinnamaldehyde on uropathogenic *Escherichia coli*. J Urol, 2010; 184:358–63; doi:10.1016/j.juro.2010.03.006.

Ardalani H, Hassanpour Moghadam M, Hadippanah A, Fotovat F, Azizi A, Soltani J. Identification and characterization of chemical composition of *Rhus coriaria* L. fruit from Hamadan, Western Iran. J Med Herbs, 2016; 6:195–8.

Ayandele A, Oladipo E, Oyeibisi O, Kaka M. Prevalence of multi-antibiotic resistant *Escherichia coli* and *Klebsiella* species obtained from a Tertiary Medical Institution in Oyo State, Nigeria. Qatar Med J, 2020; 2020:9; doi:10.5339/qmj.2020.9.

Baldiris-Avila R, Montes-Robledo A, Buelvas-Montes Y. Phylogenetic classification, biofilm-forming capacity, virulence factors, and antimicrobial resistance in uropathogenic *Escherichia coli* (UPEC). Curr Microbiol, 2020; 77:3361–70; doi:10.1007/s00284-020-02173-2.

Ballesteros-Monreal MG, Mp Arenas-Hernández M, Enciso-Martínez Y, Martínez-De La Peña CF, Del C Rocha-Gracia R, Lozano-Zarain P, Navarro-Ocaña A, Martínez-Laguna Y, de la Rosa-López R. Virulence and resistance determinants of uropathogenic *Escherichia coli* strains isolated from pregnant and non-pregnant women from two states in Mexico. Infect Drug Resist, 2020; 13:295–310; doi:10.2147/IDR.S226215.

Balouiri M, Sadiki M, Ibsouda SK. Methods for *in vitro* evaluating antimicrobial activity: a review. J Pharm Anal, 2016; 6:71–9; doi:10.1016/j.jpha.2015.11.005.

Basak S, Singh P, Rajurkar M. Multidrug resistant and extensively drug resistant bacteria: a study. J Pathog, 2016; 2016:1–5; doi:10.1155/2016/4065603.

Bauer AW, Kirby WMM, Sherris JC, Turck M. Antibiotic susceptibility testing by a standardized single disk method. Am J Clin Pathol, 1966; 45:493–6; doi:10.1093/ajcp/45.4.493.

Beretta G, Rossoni G, Santagati NA, Facino RM. Anti-ischemic activity and endothelium-dependent vasorelaxant effect of hydrolysable tannins from the leaves of *Rhus coriaria* (Sumac) in isolated rabbit heart and thoracic aorta. Planta Med, 2009; 75:1482–8; doi:10.1055/s-0029-1185797.

Buijs J, Dofferhoff ASM, Mouton JW, Wagenvoort JHT, Van Der Meer JWM. Concentration-dependency of  $\beta$ -lactam-induced filament formation in Gram-negative bacteria. Clin Microbiol Infect, 2008; 14:344–9; doi:10.1111/j.1469-0691.2007.01940.x.

Busch A, Phan G, Waksman G. Molecular mechanism of bacterial type 1 and P pili assembly. Philos Trans R Soc A Math Phys Eng Sci, 2015; 373:20130153; doi:10.1098/rsta.2013.0153.

Chaudhary N, Narayan C, Mohan B, Taneja N. Characterization and *in vitro* activity of a lytic phage RDN37 isolated from community sewage water active against MDR Uropathogenic *E. coli*. Indian J Med Microbiol, 2021; 39:343–8; doi:10.1016/j.ijmm.2021.04.011.

CLSI. Performance standards for antimicrobial susceptibility testing. 31st edition, CLSI supplement M100, United States, 2021.

Dorota W, Marta K, Dorota TG. Effect of asiatic and ursolic acids on morphology, hydrophobicity, and adhesion of UPECs to uroepithelial cells. Folia Microbiol (Praha), 2013; 58:245–52; doi:10.1007/s12223-012-0205-7.

Dunne WM. Bacterial adhesion: seen any good biofilms lately? Clin Microbiol Rev, 2002; 15:155–66; doi:10.1128/CMR.15.2.155-166.2002.

Dziki D, Cacak-Pietrzak G, Hassoon WH, Gawlik-Dziki U, Sulek A, Różyło R, Sugier D. The fruits of sumac (*Rhus coriaria* L.) as

a functional additive and salt replacement to wheat bread. LWT, 2021; 136:110346; doi:10.1016/j.lwt.2020.110346.

Elagbar ZA, Shakya AK, Barhoumi LM, Al-Jaber HI. Phytochemical diversity and pharmacological properties of *Rhus coriaria*. Chem Biodivers, 2020; 17:e1900561; doi:10.1002/cbdv.201900561.

Evans DJ, Evans DG, Young LS, Pitt J. Hemagglutination typing of *Escherichia coli*: definition of seven hemagglutination types. J Clin Microbiol, 1980; 12:235–42; doi:10.1128/jcm.12.2.235-242.1980.

Farag MA, Fayek NM, Abou Reidah I. Volatile profiling in *Rhus coriaria* fruit (sumac) from three different geographical origins and upon roasting as analyzed via solid-phase microextraction. PeerJ, 2018; 6:e5121; doi:10.7717/peerj.5121.

Fazeli MR, Amin G, Attari MMA, Ashtiani H, Jamalifar H, Samadi N. Antimicrobial activities of Iranian sumac and avishan-e shirazi (*Zataria multiflora*) against some food-borne bacteria. Food Control, 2007; 18:646–9; doi:10.1016/j.foodcont.2006.03.002.

Gabr SA, Alghadir AH. Evaluation of the biological effects of lyophilized hydrophilic extract of *Rhus coriaria* on myeloperoxidase (MPO) activity, wound healing, and microbial infections of skin wound tissues. Evid Based Complement Altern Med, 2019; 2019:1–14; doi:10.1155/2019/5861537.

Greene SE, Hibbing ME, Janetka J, Chen SL, Hultgren SJ. Human urine decreases function and expression of type 1 pili in uropathogenic *Escherichia coli*. MBio, 2015; 6:e00820; doi:10.1128/mBio.00820-15.

Greer LG, Roberts SW, Sheffield JS, Rogers VL, Hill JB, McIntire DD, Wendel GD Jr. Ampicillin resistance and outcome differences in acute antepartum pyelonephritis. Infect Dis Obstet Gynecol, 2008; 2008:1–5; doi:10.1155/2008/891426.

Gupta K, Scholes D, Stamm WE. Increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in women. J Am Med Assoc, 1999; 281:736–8; doi:10.1001/jama.281.8.736.

Hagberg L, Jodal U, Korhonen TK, Janson GL, Lindberg U, Edan CS. Adhesion, hemagglutination, and virulence of *Escherichia coli* causing urinary tract infections. Infect Immun, 1981; 31:564–70; doi:10.1128/iai.31.2.564-570.1981.

Hart A, Nowicki BJ, Reisner B, Pawelczyk E, Goluszko P, Urvil P, Anderson G, Nowicki S. Ampicillin-resistant *Escherichia coli* in gestational pyelonephritis: increased occurrence and association with the colonization factor Dr adhesin. J Infect Dis, 2001; 183:1526–9; doi:10.1086/320196.

Hassuna NA, Khairalla AS, Farahat EM, Hammad AM, Abdel-Fattah M. Molecular characterization of extended-spectrum  $\beta$  lactamase-producing *E. coli* recovered from community-acquired urinary tract infections in Upper Egypt. Sci Rep, 2020; 10:1–8; doi:10.1038/s41598-020-59772-z.

Hrv R, Devaki R, Kandi V. Comparison of hemagglutination and hemolytic activity of various bacterial clinical isolates against different human blood groups. Cureus, 2016; 8:e489; doi:10.7759/cureus.489.

Justice SS, Hunstad DA, Cegelski L, Hultgren SJ. Morphological plasticity as a bacterial survival strategy. Nat Rev Microbiol, 2008; 6:162–8; doi:10.1038/nrmicro1820.

Kacergius T, Abu-Lafi S, Kirklauskiene A, et al. Inhibitory capacity of *Rhus coriaria* L. extract and its major component methyl gallate on *Streptococcus mutans* biofilm formation by optical profilometry: Potential applications for oral health. Mol Med Rep, 2017; 16(1):949–56. doi:10.3892/mmr.2017.6674

Khameneh B, Iranshahy M, Soheili V, Fazly Bazzaz BS. Review on plant antimicrobials: a mechanistic viewpoint. Antimicrob Resist Infect Control, 2019; 8:118; doi:10.1186/s13756-019-0559-6.

Khatoun Z, McTiernan CD, Suuronen EJ, Mah TF, Alarcon EI. Bacterial biofilm formation on implantable devices and approaches to its treatment and prevention. Heliyon, 2018; 4:1067; doi:10.1016/j.heliyon.2018.e01067.

Kisiela DI, Chattopadhyay S, Tchesnokova V, Paul S, Weissman SJ, Medenica I, Clegg S, Sokurenko EV. Evolutionary analysis points to divergent physiological roles of Type 1 Fimbriae

- in *Salmonella* and *Escherichia coli*. MBio, 2013; 4:e00625–12; doi:10.1128/mBio.00625-12.
- Kirmusaoğlu S. The methods for detection of biofilm and screening antibiofilm activity of agents. Antimicrobials, antibiotic resistance, antibiofilm strategies and activity methods. IntechOpen, 2019; doi:10.5772/intechopen.84411.
- Kot B. Antibiotic resistance among uropathogenic *Escherichia coli*. Polish J Microbiol, 2019; 68:403–15; doi:10.33073/pjm-2019-048.
- Kothari V, Gupta A, Naranawal M. Comparative study of various methods for extraction of antioxidant and antibacterial compounds from plant seeds. J Nat Remedies, 2012; 12/2:162–73; doi:10.18311/jnr/2012/271.
- Krasowska A, Sigler K. How microorganisms use hydrophobicity and what does this mean for human needs? Front Cell Infect Microbiol, 2014; 4:112; doi:10.3389/fcimb.2014.00112.
- Kurek A, Grudniak AM, Szwed M, Klicka A, Samluk L, Wolska KI, Janiszowska W, Popowska M. Oleonic acid and ursolic acid affect peptidoglycan metabolism in *Listeria monocytogenes*. Antonie van Leeuwenhoek, 2010; 97:61–8; doi:10.1007/s10482-009-9388-6.
- Lagha R, Ben Abdallah F, AL-Sarhan B, Al-Sodany Y. Antibacterial and biofilm inhibitory activity of medicinal plant essential oils against *Escherichia coli* isolated from UTI patients. Molecules, 2019; 24:1161; doi:10.3390/molecules24061161.
- Lara VM, Carregaro AB, Santurio DF, de Sá MF, Santurio JM, Alves SH. Antimicrobial susceptibility of *Escherichia coli* strains isolated from *Alouatta* spp. feces to essential oils. Evid Based Complement Alternat Med, 2016; 2016:1643762; doi:10.1155/2016/1643762.
- Lodhia S, Sharaf A, Foley C. Management of recurrent urinary tract infections in adults. Surg, 2020; 38:197–203; doi:10.1016/j.mpsur.2020.01.012.
- Mahdavi S. Antimicrobial and antioxidant activities of Iranian sumac (*Rhus coriaria* L.) fruit ethanolic extract. J Appl Microbiol Biochem, 2018; 02:5; doi:10.21767/2576-1412.100021.
- Mandal SM, Dias RO, Franco OL. Phenolic compounds in antimicrobial therapy. J Med Food, 2017; 20:1031–8; doi:10.1089/JMF.2017.0017.
- Mikcha JMG, Piantino Ferreira AJ, Astolfi Ferreira CS, Yano T. Hemagglutinating properties of *Salmonella enterica* serovar enteritidis isolated from different sources. Brazilian J Microbiol, 2004; 35:54–8; doi:10.1590/S1517-83822004000100008.
- Mohammadi S, Zarei M, Zarei MM, Salehi I. Effect of hydroalcoholic leaves extract of *rhus coriaria* on pain in male rats. Anesthesiol Pain Med, 2016; 6:e32128; doi:10.5812/aapm.32128.
- Möllerby R, Källénius G, Svenson SB, Korhonen TK, Winberg J. P-fimbriae of pyelonephritogenic *Escherichia coli*: detection in clinical material by a rapid receptor-specific agglutination test. Infection, 1983; 11:68–72; doi:10.1007/BF01651363.
- Mrázková J, Malinová L, Wimmerová M. Microscopy examination of red blood and yeast cell agglutination induced by bacterial lectins. PLoS One, 2019; 14:e0220318; doi:10.1371/journal.pone.0220318.
- Nasar-Abbas SM, Halkman AK. Antimicrobial effect of water extract of sumac (*Rhus coriaria* L.) on the growth of some food borne bacteria including pathogens. Int J Food Microbiol, 2004; 97:63–9; doi:10.1016/j.ijfoodmicro.2004.04.009.
- Negus M, Phillips C, Hindley R. Recurrent urinary tract infections: a critical review of the currently available treatment options. Obstet Gynaecol, 2020; 22:115–21; doi:10.1111/tog.12644.
- Nikaido H. Multidrug resistance in bacteria. Annu Rev Biochem, 2009; 78:119–46; doi:10.1146/annurev.biochem.78.082907.145923.
- Nizet V, Varki A, Aebi M. Microbial Lectins: Hemagglutinins, Adhesins, and Toxins. In: Varki A, Cummings RD, Esko JD, et al., eds. Essentials of Glycobiology. 3rd ed. Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press, 2017; 481–91.
- Osundiya O, Oladele R, Oduyebo O. Multiple antibiotic resistance (MAR) indices of *Pseudomonas* and *Klebsiella* species isolates in Lagos University Teaching Hospital. African J Clin Exp Microbiol, 2013; 14:164–8; doi:10.4314/ajcem.v14i3.8.
- Packiavathy IASV, Priya S, Pandian SK, Ravi AV. Inhibition of biofilm development of uropathogens by curcumin—an anti-quorum sensing agent from *Curcuma longa*. Food Chem, 2014; 148:453–60; doi:10.1016/j.foodchem.2012.08.002.
- Pourahmad J, Eskandari MR, Shakibaei R, Kamalinejad M. A search for hepatoprotective activity of aqueous extract of *Rhus coriaria* L. against oxidative stress cytotoxicity. Food Chem Toxicol, 2010; 48:854–8; doi:10.1016/j.fct.2009.12.021.
- Ravindran PN, Pillai GS, Divakaran M. Other herbs and spices: mango ginger to wasabi. Handbook of herbs and spices. Elsevier, Vol. 2, pp 557–82, 2012; doi:10.1533/9780857095688.557.
- Reidel RVB, Cioni PL, Majo L, Pistelli L. Evolution of volatile emission in *Rhus coriaria* organs during different stages of growth and evaluation of the essential oil composition. Chem Biodivers, 2017; 14:e1700270; doi:10.1002/cbdv.201700270.
- Rodríguez-Pérez C, Quirantes-Piné R, Uberos J, Jiménez-Sánchez C, Peña A, Segura-Carretero A. Antibacterial activity of isolated phenolic compounds from cranberry (*Vaccinium macrocarpon*) against *Escherichia coli*. Food Funct, 2016; 7:1564–73; doi:10.1039/c5fo01441g.
- Ruiz V, Rodríguez-Cerrato V, Huelves L, Del Prado G, Naves P, Ponte C, Soriano F. Adherence of *Streptococcus pneumoniae* to polystyrene plates and epithelial cells and the antiadhesive potential of Albumin and Xylitol. Pediatr Res, 2011; 69:23–7; doi:10.1203/PDR.0b013e3181fed2b0.
- Sáez-Llorens X, McCracken GH. Clinical pharmacology of antibacterial agents. Infectious diseases of the fetus and newborn infant. Elsevier, pp 1223–67, 2006; doi:10.1016/B0-72-160537-0/50039-6.
- Sakhr K, El Khatib S. Physicochemical properties and medicinal, nutritional and industrial applications of Lebanese Sumac (Syrian Sumac - *Rhus coriaria*): a review. Heliyon, 2020; 6:e03207; doi:10.1016/j.heliyon.2020.e03207.
- Samoilova Z, Smirnova G, Muzyka N, Oktyabrsky O. Medicinal plant extracts variously modulate susceptibility of *Escherichia coli* to different antibiotics. Microbiol Res, 2014; 169:307–13; doi:10.1016/j.micres.2013.06.013.
- Scharf B, Sendker J, Dobrindt U, Hensel A. Influence of cranberry extract on Tamm-Horsfall protein in human urine and its antiadhesive activity against uropathogenic *Escherichia coli*. Planta Med, 2019; 85:126–38; doi:10.1055/a-0755-7801.
- Shabbir A. *Rhus coriaria* Linn, a plant of medicinal, nutritional and industrial importance: a review. J Anim Plant Sci, 2012; 22:505–12.
- Shaheen G, Akram M, Jabeen F, Ali Shah SM, Munir N, Daniyal M, Riaz M, Tahir IM, Ghauri AO, Sultana S, Zainab R, Khan M. Therapeutic potential of medicinal plants for the management of urinary tract infection: a systematic review. Clin Exp Pharmacol Physiol, 2019; 46:613–24; doi:10.1111/1440-1681.13092.
- Shareef HA, Abdulla ET, Mostafa ZN. Hemagglutination properties of some intestinal bacterial pathogens isolated from clinical samples. Tikrit J Pure Sci, 2010; 15:5–10.
- Shelef LA. Antimicrobial effects of spices. J Food Saf, 1984; 6:29–44; doi:10.1111/j.1745-4565.1984.tb00477.x.
- Shidfar F, Rahideh ST, Rajab A, Khandozi N, Hosseini S, Shidfar S, Mojab F. The effect of Sumac *Rhus coriaria* L. powder on serum glycemic status, ApoB, ApoA-I and total antioxidant capacity in type 2 diabetic patients. Iran J Pharm Res, 2014; 13:1249–55; doi:10.22037/ijpr.2014.1585.
- Simo M. Recent trends in biofilm science and technology. Elsevier, 2020; doi:10.1016/C2018-0-05115-4.
- De Souza GM, Neto ERDS, da Silva AM, Iacia MVM de S, Rodrigues MVP, Pereira VC, Winkelstroter LK. Comparative study of genetic diversity, virulence genotype, biofilm formation and antimicrobial resistance of uropathogenic *Escherichia coli* (UPEC) isolated from nosocomial and community acquired urinary tract infections. Infect Drug Resist, 2019; 12:3595–606; doi:10.2147/IDR.S228612.
- Stærk K, Khandige S, Kolmos HJ, Möller-Jensen J, Andersen TE. Uropathogenic *Escherichia coli* express type 1 Fimbriae only in surface adherent populations under physiological growth conditions. J Infect Dis, 2016; 213:386–94; doi:10.1093/infdis/jiv422.

Szakiel A, Ruszkowski D, Grudniak A, Kurek A, Wolska KI, Doligalska M, Janiszowska W. Antibacterial and antiparasitic activity of oleanolic acid and its glycosides isolated from marigold (*Calendula officinalis*). *Planta Med*, 2008; 74:1709–15; doi:10.1055/s-0028-1088315.

Takó M, Kerekes EB, Zambrano C, Kotogán A, Papp T, Krisch J, Vágvölgyi C. Plant phenolics and phenolic-enriched extracts as antimicrobial agents against food-contaminating microorganisms. *Antioxidants* (Basel), 2020; 9:165; doi:10.3390/antiox9020165.

Terlizzi ME, Griboaldo G, Maffei ME. UroPathogenic *Escherichia coli* (UPEC) infections: virulence factors, bladder responses, antibiotic, and non-antibiotic antimicrobial strategies. *Front Microbiol*, 2017; 8:1566; doi:10.3389/fmicb.2017.01566.

Titilawo Y, Sibanda T, Obi L, Okoh A. Multiple antibiotic resistance indexing of *Escherichia coli* to identify high-risk sources of faecal contamination of water. *Environ Sci Pollut Res*, 2015; 22:10969–80; doi:10.1007/s11356-014-3887-3.

Tohma H, Altay A, Köksal E, Gören AC, Gülçin İ. Measurement of anticancer, antidiabetic and anticholinergic properties of sumac (*Rhus coriaria*): analysis of its phenolic compounds by LC–MS/MS. *J Food Meas Charact*, 2019; 13:1607–19; doi:10.1007/s11694-019-00077-9.

Vahid-Dastjerdi E, Sarmast Z, Abdolazimi Z, Mahboubi A, Amdjadi P, Kamalinejad M. Effect of *Rhus coriaria* L. water extract on five common oral bacteria and bacterial biofilm formation on orthodontic wire. *Iran J Microbiol*, 2014; 6:269–75.

Vasudevan S, Thamil Selvan G, Bhaskaran S, Hari N, Solomon AP. Reciprocal cooperation of type A procyanidin and nitrofurantoin against multi-drug resistant (MDR) UPEC: a pH-dependent study. *Front Cell Infect Microbiol*, 2020; 10:421; doi:10.3389/fcimb.2020.00421.

Wiegand I, Hilpert K, Hancock REW. Agar and broth dilution methods to determine the minimal inhibitory concentration (MIC) of

antimicrobial substances. *Nat Protoc*, 2008; 3:163–75; doi:10.1038/nprot.2007.521.

Zalewska-Piątek BM, Piątek RJ. Alternative treatment approaches of urinary tract infections caused by uropathogenic *Escherichia coli* strains. *Acta Biochim Pol*, 2019; 66:129–38; doi:10.18388/abp.2018\_2787.

Zhaleh M, Sohrabi N, Zangeneh MM, Zangeneh A, Moradi R, Zhaleh H. Chemical composition and antibacterial effects of essential oil of *Rhus coriaria* fruits in the West of Iran (Kermanshah). *J Essent Oil Bearing Plants*, 2018; 21:493–501; doi:10.1080/0972060X.2018.1462739.

Zhong ZX, Cui ZH, Li XJ, Tang T, Zheng ZJ, Ni WN, Fang LX, Zhou YF, Yu Y, Liu YH, Liao XP, Sun J. Nitrofurantoin combined with amikacin: a promising alternative strategy for combating mdr uropathogenic *Escherichia coli*. *Front Cell Infect Microbiol*, 2020; 10:811; doi:10.3389/fcimb.2020.608547.

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