AMB Express

ORIGINAL ARTICLE Open Access

Antibacterial and antioxidant properties of sumac extract on methicillin-resistant *Staphylococcus aureus*

Nafiseh Farazandehnia[1], Farzaneh Sotoudegan[2], Abbas Akhavan Sepahy[1*] and Mohamad Reza Fazeli[2,3*]

Abstract

The research aimed to evaluate the antioxidative and antibacterial characteristics of aqueous sumac extract on methicillin-resistant *Staphylococcus aureus* through in-vitro and in-vivo study. Sumac extract has been obtained through the soaking method, and its antioxidant properties were gauged using the DPPH free radical scavenging method. The minimum inhibitory concentration (MIC) of sumac extract was determined on *S. aureus* obtained from hospitalized patients, as well as an assessment of biofilm-formation and the release of bacterial intracellular compounds. in vivo experimentation involved injecting bacteria (10^8 cfu/ml) into mice, which subsequently manifested indicators of symptoms of infection, and the number of bacteria within their bloodstream was quantified. The Sumac extract demonstrated strong antioxidant properties at concentrations of 1000 mg/ml. Furthermore, the agar tests for the gram staining, mannitol, coagulase, and DNase revealed that 190 cultured bacteria samples were identified as *Staphylococcus aureus*. These bacteria were resistant to clindamycin, ciprofloxacin, and methicillin antibiotics, but sensitive to erythromycin and penicillin antibiotics. Additionally, the bacteria displayed significant methicillin resistance and formed a strong biofilm (65.78%). The sumac extract showed a MIC range of 125–1000 µg/ml against *Staphylococcus aureus*. Treatment with concentrations above the MIC was found to prevent the formation of biofilm and increase the release of bacterial intracellular compounds. Sumac extract led to a decrease in bacterial count in the blood of mice and reduced signs of infection. Sumac extract demonstrated powerful antioxidant and antibacterial effects against resistant microorganisms, suggesting its potential as a promising compound for the treatment of resistant infections in future research.

Keywords Sumac, Methicillin-resistant *Staphylococcus aureus* (MRSA), Antioxidant, Biofilm

*Correspondence:
Abbas Akhavan Sepahy
A_akhavan@iau.ac.ir
Mohamad Reza Fazeli
fazelimo@sina.tums.ac.ir
[1]Department of Microbiology, Faculty of Biological Science, North of Tehran Branch, Islamic Azad University, Tehran, Iran
[2]Quality Control of Medicines and Supplements Group, Pharmaceutical Quality Assurance Research Center, The Institute of Pharmaceutical Sciences (TIPS), Tehran University of Medical Sciences, Tehran, Iran
[3]Department of Drug and Food Control, Pharmaceutical Quality Assurance Center, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Abbas Akhavan Sepahy, Iran

Introduction

Over the past four decades, the pharmaceutical industry has witnessed the production of numerous novel antibiotics, yet their rampant and indiscriminate usage has expedited the development of microbial resistance. A sobering 2019 report presented to the United Nations prognosticates those infections resulting from antibiotic-resistant bacteria will be responsible for an estimated 10 million annual fatalities and portend an economic crisis akin to the global financial collapse of 2008–2009 by the year 2050 (Carr et al. 2019). Antimicrobial resistance (AMR) can be ascribed to microorganisms through the mechanisms of genetic mutation and horizontal gene transfer (HGT), facilitated by various genetic elements such as chromosomes, plasmids, transposons, and other mobile genetic entities (Giedraitienė et al. 2011). In response to this burgeoning global challenge, the World Health Organization (WHO) promulgated the Global Priority Pathogen List (PPL) in 2018, aimed at offering essential guidance to researchers involved in the exploration and development of novel antibiotics (Shrivastava et al. 2018). Of particular significance within the sphere of antimicrobial resistance is *Staphylococcus aureus* (*S. aureus*), a bacterium renowned for its pivotal role. Statistics derived from the European Center for Disease Prevention and Control underscore the profound impact of hospital-acquired infections, afflicting approximately 3 million individuals annually, with an approximate fatality count of 50,000. Notably, multidrug-resistant staphylococci constitute one of the predominant etiological agents of nosocomial infections (Wojtunik et al. 2014).

S. aureus, a Gram-positive, spheroidal bacterium (coccus), has the capacity to induce infections on medical implants and generate biofilms, presenting formidable challenges in the context of antibiotic-based treatment modalities. Furthermore, approximately 25% of *S. aureus* strains are known to secrete the exotoxin TSST-1, thereby serving as the etiological agent for toxic shock syndrome (Pendleton et al. 2013). Consequently, the imperative for novel therapeutic approaches and compounds aimed at mitigating the predicaments wrought by bacterial resistance is more compelling than ever. In light of the fact that *S. aureus* has adeptly deployed an array of strategies to withstand an extensive spectrum of antibiotics, the exploration of alternative compounds capable of vanquishing infections triggered by this pathogen assumes a pivotal role in the endeavor to combat these recalcitrant microorganisms.

In contemporary pharmacology, a substantial proportion of pharmaceutical agents either trace their origins to natural sources or undergo chemical transformations or synthesis of natural compounds (Calcaterra et al. 2018). Recent scientific investigations have unveiled the noteworthy role that plant-derived antimicrobial compounds can assume in thwarting the proliferation of bacterial pathogens (Gupta et al. 2020). Natural antimicrobial products have garnered considerable scientific interest owing to their pronounced chemical diversity and inherent bioactive properties. Consequently, the exploration of their therapeutic potential has witnessed a notable surge in recent years. One of the botanical specimens that has attracted significant attention in the realm of antimicrobial research is the sumac plant, scientifically denoted as *Rhus coriaria*. Numerous studies have substantiated its antimicrobial attributes (Ghane et al. 2022). Nevertheless, an area that has not been extensively scrutinized pertains to the impact of sumac aqueous extract on antibiotic-resistant bacterial strains. This study seeks to address this knowledge gap by assessing the antioxidant and antibacterial effects of sumac aqueous extract on *S. aureus*, a bacterium implicated in hospital-acquired infections and resistant to methicillin. The assessment will be conducted through the utilization of both in vitro and in vivo methods, employing a murine animal model as the experimental platform.

Materials and methods

Plant material

In the current investigation, Tabriz sumac, denoted by the scientific nomenclature *Rhus coriaria* and recognized as the superior species of the sumac genus, was diligently procured from the Horand region situated in the northeastern precinct of East Azarbaijan province. The geographical coordinates for this collection site were specified as longitude 47°E and latitude 38°N, characterized by elevations ranging from 650 to 1900 m above sea level. Subsequently, the gathered samples were identified and the voucher specimen (HE4-Z-TEH) was deposited at the Herbarium of the Faculty of Pharmacy in Tehran University of Medical Sciences (Tehran, Iran).

Chemical and reagents

Blood Agar, Muller Hinton Agar, Broth trypticase culture medium, Brain Heart Infusion Agar, Nutrient Broth, Brain Heart Infusion Broth obtained from Merck Company (Darmstadt, Germany). Coagulase test kit, Antibiotic disk was procured from Nik Azma (Tehran, Iran). Methicillin was provided by Sigma-Aldrich, located in Missouri, USA. Merck Company (Darmstadt, Germany) supplied all the other materials.

Preparation of aqueous sumac extract

Following the meticulous separation and purification of sumac seeds, they were finely milled utilizing an electric mill, bearing the brand Bekordane, a product originating from Iran. Notably, 50 g of the ground sumac seed powder were subsequently introduced into a sterile receptacle, and this was supplemented with 950 ml of sterile

deionized water. The mixture was continuously stirred for 1 h at 40 °C. Thereafter, it was subjected to thermal treatment at 100 °C for a 2 min interval. After cooling, the solution underwent four rounds of filtration, culminating in a final filtration step employing a millipore filter, facilitated by a vacuum pump. The filtrate was subjected to centrifugation, with a 30 min cycle at speeds ranging from 2000 to 4000 rpm. The sedimented supernatant, which exhibited clarified characteristics, was separated from the centrifuge and subjected to further filtration using sterile cellulose nitrate filters, characterized by a porosity of 0.8 nm. A final filtration operation, employing a sterile filter with a porosity of 0.22 nm, was executed to ensure the complete removal of particulate matter and bacteria from the solution, thus yielding an exclusive extract. The procedure occurred under aseptic conditions (Adwan et al. 2015).

GC-MS analysis

The active constituents were separated and quantified using the UltraFast TRACE GC system (Thermo Scientific, Co.). GC-MS analysis was conducted on a Perkin-Elmer GC Clarus 500 system, which includes an AOC-20i autosampler and a gas chromatograph interfaced to a Mass Spectrometer (GC-MS) equipped with an Elite-5MS (5% diphenyl/95% dimethyl polysiloxane) fused capillary column (30×0.25 µm ID × 0.25 µm df). For GC-MS detection, an electron ionization system operated in electron impact mode with an ionization energy of 70 eV. Helium gas (99.999%) served as the carrier gas at a constant flow rate of 1 ml/min, and an injection volume of 2 µL was used (a split ratio of 10:0). The injector temperature was maintained at 250 °C, the ion-source temperature at 200 °C, and the oven temperature was programmed from 110 °C (isothermal for 2 min) with a subsequent increase of 10 °C/min to 200 °C, followed by an increase of 5 °C/min to 280 °C, and ending with a 9 min isothermal at 280 °C.

Mass spectra were recorded at 70 eV, with a scan interval of 0.5 s and fragments ranging from 45 to 450 Da.

Investigating the antioxidant properties of sumac aqueous extract

The assessment of sumac's antioxidant capacity was executed employing the DPPH free radical scavenging methodology. The DPPH radical scavenging percentage was computed in accordance with the formula outlined by Özcan (2003).

$$\text{Scavenging activity } (\%) = \frac{\text{Absorption of control} - \text{Absorption of sample}}{\text{Absorption of control}} \times 100$$

The IC_{50} level represents the concentration of the extract composition required to scavenge 50% of the free radicals. The IC_{50} values of the samples were compared with the IC50 values of reference substances such as ascorbic acid, quercetin, or butylated hydroxyanisole (BHA). To quantify the antioxidant activity of the sumac aqueous extract, 4 ml of the extract was dispensed into test tubes, and subsequently, 1 ml of the DPPH solution was added to each test tube. The contents of all tubes were meticulously vortexed, ensuring thorough homogenization, and then left to incubate for a period of 30 min, maintained at room temperature under conditions of subdued lighting The absorbance of the samples was recorded at a wavelength of 817 nm, utilizing a UV-Vis spectrophotometer (Shimadzu 1900i, Japan). As a positive control, Butylated hydroxytoluene (BHT) was employed (Özcan et al. 2003).

Investigation of the antibacterial effect of sumac aqueous extract on *S. aureus*

Sampling

A total of 300 clinical specimens were collected from patients presenting with a diverse array of infections at several healthcare facilities in Tehran, including Imam Khomeini Hospital, Nikan Hospital, Day Hospital, Shahid Labafinejad Hospital, Milad Hospital, Sina Hospital, Erfan Hospital, Firozabadi Hospital, Shahadai Tajrish Hospital, and the Third Hospital of Shaaban. These patients, who had sought medical care at the respective hospital clinics, displayed clinical symptoms indicative of infectious conditions, encompassing manifestations such as fever, fatigue, diarrhea, muscle pain, and cough, among others. The specimens were procured from the infection sites using sterile swabs and subsequently transported to the laboratory for analysis. Importantly, it is noteworthy that the research endeavors adhered to ethical standards, with approval granted and registration under the code of ethics IR.IAU.ZANJANREC.96,12 to facilitate the conduct of all experiments.

Sample preparation and diagnosis of S. aureus resistant to methicillin

For the isolation of *S. aureus* bacteria, a volume of 0.1 ml from the samples, suspended in tryptic soy broth (TSB) culture medium, was aseptically transferred onto blood agar culture medium and subsequently incubated at 37 °C for a duration of 24 h (Arena et al. 2022). *S. aureus* bacteria were identified using a range of phenotypic and biochemical tests, including the Gram staining test, the menthol test, the DNase agar test, and the tube coagulase test (Nouwen et al. 2004).

Determining antibiotic sensitivity by disc diffusion method

To ensure the integrity and quality of the antibiotic discs prior to their application in the test, a subset of the

microbial suspension derived from the samples, in conjunction with the standard *S. aureus* strain (ATCC29213) at the standard concentration of 1×10^8 McFarland CFU/ml, was cultured on Mueller Hinton agar culture medium. Following this, antibiotic discs, including oxacillin (1 µg), penicillin (10 µg), gentamicin (10 µg), ciprofloxacin (5 µg), erythromycin (15 µg), and clindamycin (2 µg), were placed at equidistant intervals of 22 mm from one another and positioned at a distance of 16 mm from the periphery of the culture plate. Subsequently, the plates were incubated at 37 °C for a duration of 24 h. The diameter of the zone of inhibition surrounding each antibiotic disc was meticulously measured using a ruler and then compared with the Clinical and Laboratory Standards Institute (CLSI) guidelines for each antibiotic disc to validate the quality (Gündoğan et al. 2006).

Confirmation of resistance to methicillin in cultured strains by phenotypic method

To corroborate the resistance of the bacteria to methicillin, oxacillin was employed as it represents a more resilient member of the same antibiotic class. In pursuit of this objective, a minor portion of nascent bacterial colonies (cultured for 24 h) was aseptically harvested and subsequently subcultured using a sterile inoculating needle. Thereafter, various concentrations of oxacillin (0.125, 0.155, 0.200, and 0.256 µg/ml) were incorporated into the Mueller Hinton agar culture medium. In accordance with the criteria established by the CLSI guidelines from 2016, the growth of at least two bacterial colonies in the culture medium was indicative of bacterial resistance to methicillin.

Biofilm formation test

Biofilm formation was assessed using the microtiter plate method (Acharya et al. 2018). Initially, a portion of the recently established bacterial colony was subcultured in a culture medium, specifically TSB, and maintained for 24 h at 37 °C in test tubes. Subsequently, the culture medium containing bacteria was subjected to centrifugation at 3000 rpm for a duration of 10 min. The removal of the supernatant, 5 ml of sterile culture medium was introduced into the tubes. The optical density of the solution within the tubes was standardized to 1 at a wavelength of 595 nm. Following this calibration, the suspension was diluted to a ratio of 1:40 using sterile TSB culture medium. Next, 200 µl of the diluted suspension were aseptically inoculated into a 12-well microplate featuring a flat bottom. For the purpose of establishing a negative control, sterile TBS medium devoid of bacteria was employed. The microplates were subsequently incubated at 37 °C for a duration of 24 h. post-incubation, the microplates underwent three cycles of thorough washing with sterile phosphate buffer saline (PBS), following which they were inverted and allowed to air-dry for 2 h at room temperature.

Subsequently, 200 µl of a 0.2% solution of crystal violet dye were added to the microplates and kept at a temperature of 37 °C for 15 min. Afterward, the microplates were carefully washed three times with distilled water. In an effort to fix the dye, which had become bound to the biofilm-forming bacteria, a solution consisting of 80% ethanol and 20% acetone (v/v) was introduced into the wells of the microplates. The optical absorbance of the microplates was then recorded at a wavelength of 595 nm, and the optical absorption values were calculated using a specific formula.

Optical absorbance (ODc) = average optical absorbance of negative control (OD) + (standard deviation (SD) of negative control x 3) OD < ODc: no biofilm formation, ODc < OD < 2ODc: weak biofilm, 2ODc < OD < 4ODc: moderate biofilm, OD > 4ODc: strong biofilm.

Determination of the minimum inhibitory concentration of sumac aqueous extract against the drug resistant bacterial isolates and biofilm formation

To ascertain the MIC, a series of ten successive dilutions for the sumac aqueous extract were meticulously prepared. Initially, a stock solution with a concentration of 37.6 mg/ml was prepared. Subsequent to thorough vortexing, serial dilution was performed till concentration 0.3 mg/ml (Tendolkar et al. 2004). It is essential to mention that each of these tubes was inoculated with an approximate quantity of 10 (cfu/ml) of *S. aureus* bacteria. Following an incubation period of 24 h, the tubes were systematically examined, commencing with the tube featuring the lowest extract concentration and progressing toward the tube with the highest concentration. The initial tube displaying no turbidity attributed to microbial proliferation was documented as the MIC (Ignaciuk et al. 2006). To assess the impact of sub-MIC of the sumac aqueous extract on biofilm formation, the microtiter plate biofilm formation assay was conducted (Fazeli et al. 2007).

Examination of the release of bacterial intracellular compounds

The optical density of cultured *S. aureus* bacteria, which had been grown for 18–20 h, was measured by a UV spectrophotometer set at 600 nm. The culture was then centrifuged at 5000 rpm for 10 min. After each centrifugation, the pellet was carefully washed with 0.1 M PBS, pH: 7. subsequently, the culture was exposed to the MIC of the sumac extract and incubated in a shaker for 1 h at 37 °C. Following this incubation, the culture was centrifuged once again for 2 min at 12,000 rpm (Rhayour et al. 2002).

Ultimately, the optical density of the resulting supernatant was recorded using a spectrophotometer UV at a 260 nm wavelength. At the same time, a control experiment was carried out, involving 0.1 M PBS at pH: 7, along with the antimicrobial substances at their respective MIC, in the absence of bacteria, enabling a clear differentiation between these conditions. Additionally, 0.1 M PBS at pH: 7 was utilized as a control reference point.

Investigating the antiviral effect of sumac aqueous extract

Examining the cytotoxicity of sumac extract using HeLa cell culture

HeLa cell line was used for this study. HeLa cell is one of the human cervical cancer cells and is a suitable host cell for the multiplication of many viruses, including HSV-1. The above cell was obtained from the cell bank of the Pasteur Institute of Iran. The above cells were cultured in DMEM culture medium with fetal bovine serum FBS and antibiotics penicillin and streptomycin at 37 °C and 5% CO_2. Acyclovir-resistant herpes simplex virus type 1 used in this study was obtained from the Department of Virology, Terbit University, Madras. After multiplication in HeLa cell line, the above virus was titrated by Tissue Culture Infective Dose 50% (TCID50) method and kept at -70 °C for further work. To determine the cytotoxicity of sumac extract on HeLa cells, a 24-well plate containing a monolayer of the above cells was prepared and 1 ml of different concentrations of the extract (100, 200, 300, 400, 500, 600, 700, 800, 900, 1000 µg/ml) in culture medium containing 1% serum was added to different wells containing cell monolayer and 1 ml of extract-free medium containing 1% serum was added to one well for control. The above plate was incubated for 72 h in a 37 °C incubator containing 5% CO_2, and after this period, the amount of living cells was determined using trypan blue dye and Neobar slide, and the percentage of living cells in each well was calculated separately using the formula The following was calculated:

100* (number of live cells + number of dead cells/numbers of live cells) = percentage of live cells.

Investigating the effect of sumac extract on herpes simplex virus type 1

To investigate the direct effect of the extract on the virus, a cell monolayer was prepared from HeLa cells in a 24-well plate and 100 TCDI50/ml of the virus was prepared at the minimum effective cytotoxic concentration, the same work was done with the medium without the extract (for control). After 1, 2, 3 and 4 h, 200 µl of the above suspension was added separately to the cells in the wells of the 24-well plate. After 1 h of virus absorption, the supernatant of the infected cells was removed and 1 ml of culture medium containing 1% serum was added to the cells and incubated for 48 h at 37 °C and 5% CO_2. After the incubation time, the supernatant solution of the cells of each well was collected separately and titrated by the TCID 50 method.

In vivo investigation of antimicrobial activity of sumac extract

A total of 30 male NMRI mice, aged between 8 and 12 weeks and weighing between 22 and 25 g, were employed in this study. The mice were procured from the animal facility at the Faculty of Pharmacy, Tehran University of Medical Sciences. Subsequently, they were housed in standard cages, provided with both food and water, and maintained under optimal environmental conditions, these conditions adhered to a regimen of 12 h of light and 12 h of darkness, a constant temperature of 24 °C ± 2, and an approximate humidity level of 52%. The mice were segregated into six groups, each consisting of 5 individuals (Table 1). After an initial 5-day period, Groups 4, 5, and 6 received subsequent injections of the sumac extract. The dosage administered was contingent upon several factors, including the MIC, the use of gentamicin antibiotic, and the weight of the mice, with a dosage calculation of 40 mg/kg/day, as well as an interaction involving a 50/50 ratio of antibiotic and extract. The injection regimen for groups 4, 5, and 6 was as follows: Group 4 received an injection of (gentamicin + sumac extract), Group 5 was injected with gentamicin alone, and Group

Table 1 Group division for investigation of antimicrobial activity of sumac extract in mice

Groups of mice					
Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
0.1 ml injection of normal saline (as a control)	0.1 ml injection of sumac extract	0.1 ml injection of *S. aureus* bacterial suspension (10^8 cfu/ml)	0.1 ml injection of *S. aureus* bacterial suspension (10^8 cfu/ml)	0.1 ml injection of *S. aureus* bacterial suspension (10^8 cfu/ml)	0.1 ml injection of *S. aureus* bacterial suspension (10^8 cfu/ml)
After an initial 5-day period					
–	–	–	subsequent injections of (gentamicin + sumac extract)	subsequent injections of gentamycin in isolation	subsequent injections of sumac extract exclusively

6 was administered an injection of sumac extract exclusively. Subsequently, after an additional 5-day interval, blood samples were obtained from the mice via tail vein puncture for further analysis. Subsequently, the collected blood samples were diluted with 0.5 ml of normal saline solution. From this dilution, 0.1 ml aliquots were cultured on nutrient agar (NA) and mannitol salt agar (MSA) to facilitate the identification of bacteria introduced into the mice via the administration of *S. aureus* and their subsequent treatment with sumac extract. The enumeration of bacteria in the blood samples obtained from the mice was also a key focus of the investigation. It is worth noting that the research protocol adhered to international standards governing the use of laboratory animals, and it was conducted in accordance with ethical principles, as delineated by the code of ethics IR.IAU.ZANJANREC.96,12. The study was reviewed and granted approval by the university's ethics committee. Moreover, the injections were administered subcutaneously to the six designated groups, in accordance with the prescribed injection schedule.

Statistical analysis

The normality of the data was assessed employing the Shapiro-Wilk test. To compare the data from the experiments, t-tests and Mann-Whitney U tests were employed. All data analyses and graphical representations were conducted using SPSS version 24. The significance level set for the tests was 0.05, with a corresponding confidence level of 95%.

Results

Extraction from sumac seeds

The chemical composition of the Sumac extraction is presented in Table 2. The GC–MS analyses of samples (Fig. 1S) revealed the presence of a total of 40 components. The most abundant compound in this extract was B-caryophyllene, followed by the Thunbergene.

Antioxidant properties of sumac aqueous extract

The results of the antioxidant activity assay revealed a direct correlation between the concentration of the sumac extract and BHT with the level of antioxidant activity. Notably, the highest degree of antioxidant activity was observed at a concentration of 1000 mg/ml, while the lowest level of antioxidant activity was documented at a concentration of 50 mg/ml (Table 3).

Investigating the antimicrobial properties of sumac aqueous extract

Phenotypic tests for bacteria detection

The phenotypic tests, along with the Gram staining procedure, indicated that the cultured bacteria exhibited characteristics consistent with cocci morphology, a purple coloration, and a gram-positive staining pattern (Fig. 1), displaying a cluster-shaped configuration. Furthermore, the mannitol test results demonstrated that out of the 300 samples of *S. aureus* bacteria, 190 samples displayed growth on MSAculture medium, generating yellow bacterial colonies. In addition, the coagulase test results revealed that 190 of the isolated bacterial samples (representing 63.33% of the total) exhibited complete

Table 2 Chemical composition of sumac extract using gas chromatography method

Num	Component name	Percent of total%	*R*.T min	Num	Component name	Percent of total%	*R*.T min
1	Hexanal	0.15	5.88	21	B-caryophyllene	26.32	28.801
2	Octane	0.12	6.19	22	Geranylcetone	0.84	29.101
3	Alpha-pinene	0.68	10.33	23	x-Humulene	3.10	29.589
4	Heptenal	0.25	10.753	24	x-Amorphen	2.65	30.170
5	Furan, 2-pentyl	0.47	12.213	25	b-Selinene	1.26	30.521
6	Octanal	0.27	12.482	26	x-Muurolen	2.36	30.856
7	Limonene	0.32	13.747	27	Delta-cadinene	4.54	31.587
8	Octenal	0.39	14.575	28	Gamma-selinene	1.30	32.039
9	Nortricyclene	0.50	15.679	29	1,2,3,6 Teramethyl-z-jasmon	2.71	32.513
10	Nonanal	2.07	16.488	30	11-Diene longi flenal dehyde	0.84	33.221
11	Nonenal	0.54	18.493	31	Caryophyllene oxide	2.46	33.566
12	Terpinolene	0.50	19.938	32	n-Cetane	0.34	33.892
13	Decanal	0.83	20.229	33	Viridiflorol	1.21	34.894
14	Karvon	0.38	21.611	34	x-Guaiene	1.41	35.595
15	2-Decenal	3.38	22.506	35	Caryophyllen epoxid	0.56	35.979
16	4 – 2 Decadienal	1.19	23.483	36	Hexahydrofarnesyl acetone	0.58	40.573
17	Heptenlacrolein	2.70	24.406	37	Geranly for mate	0.70	42.651
18	Terpinolen	0.31	25.684	38	Thunbergene	25.71	43.618
19	Undecenal	1.57	26.063	39	Chrysanthone	2.15	44.076
20	Copaen	1.24	26.844	40	Cis-salvene.B.elemene	0.64	46.771

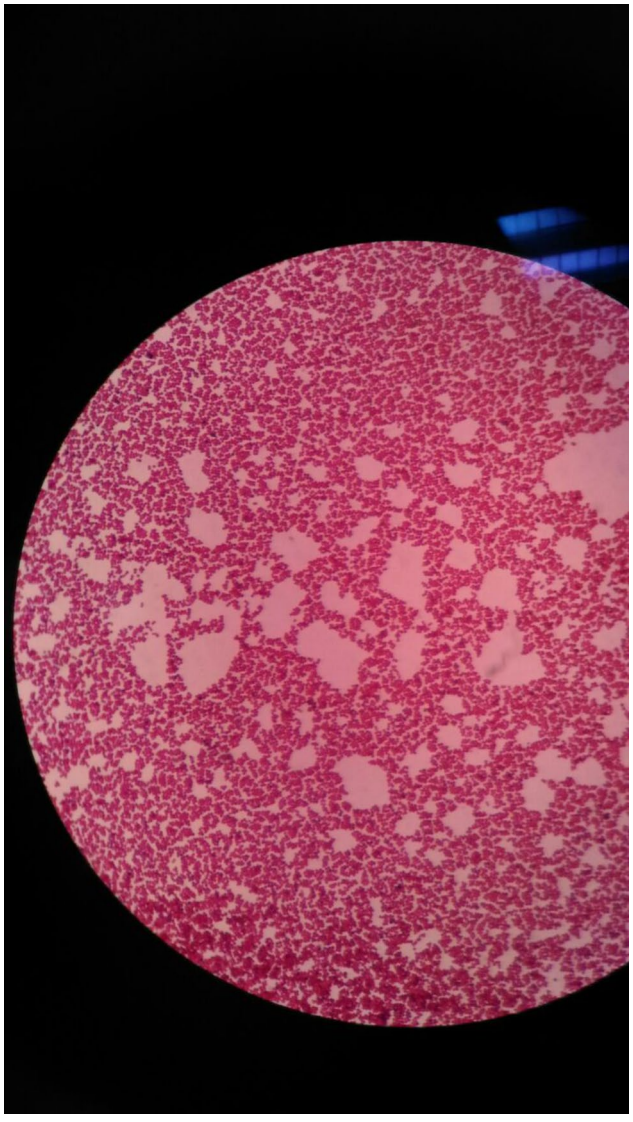

Fig. 1 Gram-positive cocci isolates

plasma coagulation, while 43 samples (constituting 14.33%) led to the formation of large continuous clots, and 31 samples (10.33%) gave rise to small, continuous clots in the plasma. The DNase agar test results indicated the presence of a distinct clear zone surrounding 211 of the cultured bacterial samples. Conversely, the DNase agar test yielded negative results for 89 of the samples.

Antibiotic sensitivity test

In the assessment of the zones of inhibition surrounding the antibiotic discs within the 190 strains identified with the *S. aureus* phenotype, it was observed that clindamycin, ciprofloxacin, and oxacillin (methicillin) exhibited the most elevated levels of antibiotic resistance. Conversely, erythromycin and penicillin antibiotics demonstrated the greatest antibiotic susceptibility among the tested strains (Table 4).

Table 4 Estimation of the number and percentage of sensitivity and resistance of *S. aureus* bacteria tested to different antibiotic discs

Antibiotics	Sensitive	Medium	Resistant
Penicillin	108 (56.84%)		82 (43.15%)
Oxacillin	57 (30%)	45 (23.68%)	88 (46.31%)
Gentamicin	63 (31.15%)	59 (31.05%)	68 (35.78%)
Erythromycin	102 (53.68%)	39 (20.52%)	49 (25.78%)
Ciprofloxacin	38 (20%)	32 (16.82%)	120 (63.15%)
Clindamycin	27 (14.21)	52 (27.34%)	111 (60.56%)

Table 5 The ability of biofilm formation in the tested *S. aureus* bacteria

Ability to form biofilm	Number and percentage of samples (%)	Optical absorbance mean (nm) ± Standard deviation (nm)
Strong biofilm	125–65–78	0.8380 ± 0.0241
Medium biofilm	45–23–68	0.5220 ± 0.0443
Weak biofilm	15–7–89	0.2490 ± 0.0212
Planktonic bacteria	5–2–63	0.2290 ± 0.0242

Confirmation of resistance to methicillin

Upon culturing 190 samples of *S. aureus* bacteria at concentrations of 0.125 and 0.155 µg/L of oxacillin, discernible differences were noted in the growth patterns of bacterial colonies. However, it is noteworthy that at the concentrations of 0.200 µg/L and 0.256 µg/L, there was a marked absence of colony growth. Consequently, the findings from the MIC test indicated that the cultured bacteria exhibited moderate to high levels of resistance to the antibiotic methicillin.

Biofilm forming ability

The majority of the cultured bacterial strains demonstrated a propensity for robust biofilm formation, with 65.78% exhibiting strong biofilm-forming capabilities, followed by 23.68% which demonstrated an intermediate level of biofilm formation. In contrast, a mere 2.63% of the strains adopted a planktonic lifestyle, manifesting a comparatively lower biofilm formation propensity (Table 5).

Table 3 Antioxidant activity of sumac aqueous extract

Sumac extract concentration (mg/ml)	50	100	200	300	400	500	1000
Antioxidant activity of Sumac extract (%)	79.66	93.1	93.65	94.08	94.64	94.86	95.25
Antioxidant activity of BHT† (%)	77.97	90.41	92.53	92.86	93.24	93.51	93.75

†BHT: hydroxytoluene Butylated

The minimum inhibitory concentration of sumac aqueous extract on S. aureus and biofilm

The findings indicate that positive biofilm-forming strains exhibited susceptibility to sumac extract at concentrations ranging 62.5–4000 µg/ml over a 24 h incubation period. Notably, the MIC values exhibited variations across different strains, with a range spanning from 125 to 1000 µg/ml, as elucidated in Table 6. For the quantitative evaluation of the anti-biofilm properties of sumac extract, the microtiter plate method was employed. The results of this assay revealed that, above the MIC of sumac extract, none of the strains were capable of forming biofilm, as delineated in Table 7. It was observed that the data presented in the table showed a reduction in the light absorption levels for all strains following treatment with sumac extract, indicating decreased bacterial growth. This reduction signifies the loss of bacterial cells' biofilm-forming capacity, rendering them unable to adhere to the microplate surface and, consequently, leading to a diminished light-absorbing capacity.

Release of intracellular compounds

The results of the release of cellular compounds showed that when the sample bacteria were exposed to sumac extract for 1 h, after the addition of the extract, the release of intracellular compounds significantly increased compared to the control group. This indicates that the damaged membrane was unable to repair, leading to bacterial cytoplasmic membrane disruption, cell lysis, and the release of most intracellular compounds (Table 8).

Investigating the antiviral effects of sumac extract

Cytotoxicity

The 50% cytotoxic concentration (CC50) value of the extract was 780 µg/ml and the minimum effective cytotoxic concentration of sumac extract was 390 µg/ml on the HeLa cell line using the dose response curve (Table 9).

The effect of sumac extract on herpes simplex virus type 1

The virus titer decreased after 1, 2, 3, and 4 h of treatment with sumac extract (390 µg/ml), compared to the controls. The most significant inactivation effect of the plant extract on the virus was observed at hours 3 and 4, with the virus titer decreasing from 5.105 TCID50/ml in the control to 5.104 TCID50/ml at those times ($P=0.003$). The results of the extract's effect on the virus at all the above times are shown in Fig. 2.

Based on the obtained results of Antiviral effect of sumac extract in different concentrations on virus multiplication, the concentration of 390 µg/ml of sumac extract had the most inhibitory effect on the proliferation of the virus ($P=0.001$) in comparison with other concentrations of extract and control (Fig. 3).

Table 6 Determination of MIC of sumac extract in different *S. aureus* isolates

Bacteria	Strain number	‡MIC (µg/ml)
S. aureus	7	1000
S. aureus	9	500
S. aureus	31	250
S. aureus	32	125
S. aureus	33	2000
S. aureus	34	500
S. aureus	43	4000
S. aureus	45	1000
S. aureus	46	250
S. aureus	47	1000
S. aureus	‡ATCC35556	2000
S. aureus	ATCC12228	500

†ATCC: American Type Culture Collection (USA)

‡MIC: Minimum Inhibitory Concentration

Table 7 Quantitative investigation of biofilm production in *S. aureus* strains treatment with concentrations higher than MIC of the extract

Bacteria	Strain number	Optical absorption	Concentration of extract
S. aureus	7	0.26	0.13
S. aureus	9	0.11	0.08
S. aureus	31	0.25	0.18
S. aureus	32	0.34	0.17
S. aureus	33	0.26	0.09
S. aureus	34	0.44	0.15
S. aureus	43	0.38	0.19
S. aureus	45	0.52	0.086
S. aureus	46	0.30	0.089
S. aureus	47	0.51	0.23
S. aureus	ATCC35556	0.48	0.082
S. aureus	ATCC12228	0.11	0.002

Table 8 Release of intracellular compounds of *S. aureus* at OD:260 nm

Samples	Compounds containing bacteria	Bacteria-free ingredients
Control	0.110 ± 0.000	–
Sumac extract (50 µg/ml)	0.190 ± 0.001	0.132 ± 0.00

OD: indicates the amount of optical absorption of the sample by the spectrophotometer

In vivo investigation of antimicrobial activity of sumac extract

In the assessment of the antimicrobial efficacy of sumac extract using an animal model, clinical manifestations such as diarrhea, dehydration, and weight loss, which are common indicators of bacteremia and infection, were observed. Hence, this study conducted a comprehensive examination of these clinical symptoms in the mice under investigation. Additionally, the research probed

Table 9 Cytotoxic effect of sumac extract against HeLa cells by trypan blue and MTT methods after 72 h. (Mean± SD; $n=3$)

Sumac extract concertation (µg/ml)	Viable cells by trypan blue method (%)	Viable cells by MTT method (%)
Control	98 ± 0.4	-
100	97 ± 0.7	96 ± 0.5
200	97 ± 1.6	95 ± 1.4
300	94 ± 1.2	95 ± 0.9
400	88 ± 1.1	89 ± 1.5
500	84 ± 1.5	79 ± 1.4
600	75 ± 1.1	70 ± 1.8
700	63 ± 1.8	61 ± 1.2
800	47 ± 1.2	48 ± 0.9
900	29 ± 1.6	25 ± 1.1
1000	8 ± 1.1	3 ± 0.8

the quantification of bacteria present in the bloodstream of the studied mice. Furthermore, a comprehensive evaluation encompassed an examination of other concurrent symptoms, such as wounds, with their findings duly reported. The results unequivocally demonstrated that the administration of sumac aqueous extract led to a noteworthy reduction in symptoms associated with *S. aureus* infection, as documented in Table 10.

Discussion

Contemporary research endeavors increasingly focus on the antioxidant and antimicrobial attributes of plant extracts, offering a promising avenue for the discovery of novel bioactive compounds with therapeutic benefits and minimal side effects. These plant-derived compounds exhibit intrinsic antimicrobial properties capable of counteracting resistance mechanisms observed in clinically resistant species, thus enhancing the susceptibility of such organisms to antibiotics (Ignaciuk et al. 2006). Notably, plant bioactive compounds can augment the effectiveness of antibiotics through various mechanisms, including facilitating their cellular entry by destabilizing the cytoplasmic membrane (Álvarez-Martínez et al. 2020), inhibiting efflux pump systems (EPs), and disrupting biofilm formation (Skariyachan et al. 2018). The present study investigates the impact of sumac aqueous extract on methicillin-resistant *S. aureus* bacteria, contributing to understanding of its potential in combating antibiotic resistance.

In this study, a phenotypic examination of 300 clinical samples led to the detection of 190 strains of *S. aureus* bacteria. These samples exhibited pronounced antibiotic resistance, most notably against clindamycin, ciprofloxacin, and oxacillin (methicillin), while showing sensitivity to erythromycin and penicillin antibiotics. Notably, the MIC test indicated that *S. aureus* samples displayed moderate to high resistance to oxacillin (methicillin). A review of the pertinent literature revealed striking similarities between these findings and those reported (Dibah et al. 2014; Arabestani et al. 2015). These results align closely with the findings of a study, which identified a frequency of methicillin-resistant strains among *S. aureus* isolates exceeding 50% (Arabestani et al. 2016). In their investigation of the frequency and antibiotic resistance patterns of MRSA strains of *S. aureus* reported that these strains displayed the highest resistance to clindamycin and ciprofloxacin, while vancomycin proved to be the most effective antibiotic (Tabaei et al. 2016), echoing the outcomes of the current study.

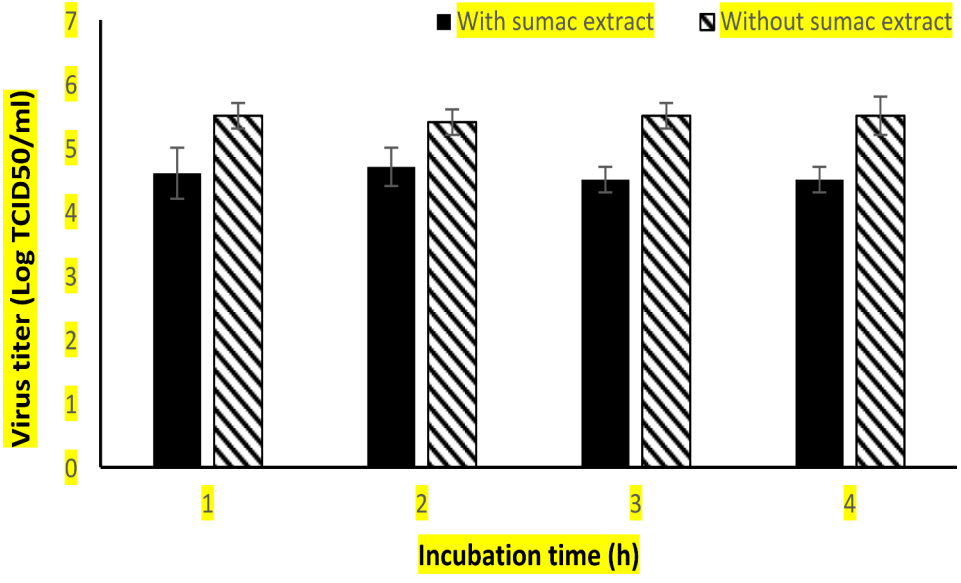

Fig. 2 Antiviral effect of sumac extract at different times on acyclovir-resistant HSV-1

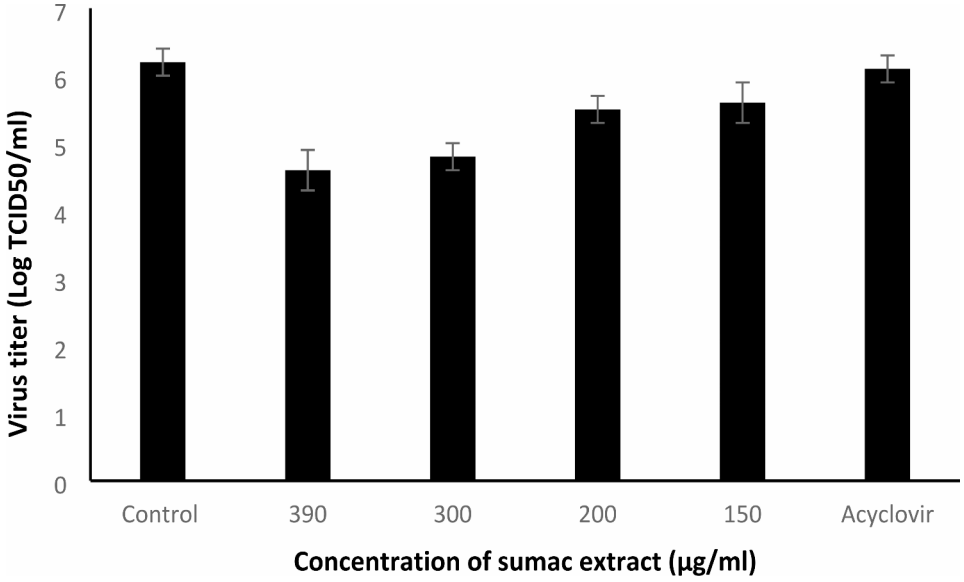

Fig. 3 Effect of different concentrations of sumac extract on acyclovir-resistant HSV-1

Table 10 Antimicrobial activity of sumac aqueous extract using the mouse animal model

Common symptoms of bacteria in the blood and the occurrence of infection in mouse					
Group number	**Diarrhea**	**Weight Loss**	**Dehydration**	**Other things**	**Bacterial count in a blood drop**
Group 1	-	-	-	-	-
Group 2	-	-	-	Injury and ulceration at the injection site	6
Group 3	+(Medium)	-	+	Decreased activity and depression	503
Group 4	+(Medium)	-	+	Decreased activity and depression death on the second, third and fourth day	141
Group 5	+,-	-	+	-	93
Group 6	-	-	-	-	-

Comparing the results from various studies, it becomes evident that the nature and prevalence of antibiotic resistance in *S. aureus* bacteria differ across regions. This variance in prevalence can be attributed to an array of factors, including substantial population migrations, differing geographical climates, the timing of sample collection during various seasons of the year, and the presence of strains with more complex genetic mutations in cities characterized by higher population density (Li et al. 2020).

Furthermore, the present study exposed the ability of the identified *S. aureus* bacteria to form biofilms. Existing research has consistently demonstrated that the presence of pathogenic bacteria within biofilm communities is intrinsically linked to the perpetuation of chronic infections. Resistance mechanisms in these bacterial biofilm communities, distinct from planktonic bacteria, include site-specific mutations, reduced cell permeability, efflux pumps, and drug-modifying enzymes, as opposed to drug-modifying proteins (Kumar et al. 2013; Lata et al. 2015; Broon et al. 2000). Hence, it becomes evident that diverse and shared mechanisms of antibiotic resistance are insufficient to elucidate the various instances of antibiotic-resistant biofilm infections (Akrayi et al. 2013). In biofilm communities, a myriad of factors contributes to this phenomenon. These include the evolution of a modified chemical microenvironment within the biofilm, the gradual or incomplete infiltration of antibiotics into the biofilm structure, as well as the development of cellular differentiation in biofilm bacteria, exemplified by the production of spores. Such intricate mechanisms confer resistance to antibiotics and undermine the effectiveness of conventional treatment modalities (Kumar et al. 2016).

In the current investigation, the results from the MIC test of the sumac aqueous extract against *S. aureus* bacteria demonstrated the robust antibacterial properties of this extract. Furthermore, the evaluation of the effect of sumac aqueous extract on the formation of biofilm by these bacteria revealed that treatment with sumac aqueous extract significantly diminished the capacity of *S.*

aureus bacteria to generate biofilm. Moreover, an assessment of the release of intracellular compounds from bacteria confirmed that treatment with sumac aqueous extract led to an augmented discharge of intracellular constituents in treated bacteria compared to the control group, substantiating the irreversible damage to the bacterial cytoplasmic membrane subsequent to treatment with the aqueous sumac extract. Based on the findings, a reduction in S. aureus growth following treatment with sumac extract was observed (MIC: 0.025%). Reports also demonstrated a decrease in the biofilm formation capacity of the tested *S. aureus* bacteria upon exposure to varying concentrations of sumac aqueous extract (Nasar-Abbas and Halkman 2004). A previous study indicated that sumac extract demonstrated notable antimicrobial effects against a range of gram-positive bacteria. Among the gram-positive bacteria tested, *S. aureus* exhibited a particularly high level of sensitivity to the antimicrobial action of sumac aqueous extract (Ahmadian-Attari et al. 2017). In a comparative study, between sumac aqueous extract and Shirazi extract on gram-positive and gram-negative pathogenic bacteria, it was found that sumac aqueous extract possessed eightfold greater antimicrobial effects than Shirazi thyme aqueous extract. Additionally, these effects were more potent against gram-negative bacteria compared to gram-positive bacteria (Fazeli et al. 2007). In another study involving *S. aureus* bacteria that were resistant to methicillin and vancomycin, the aqueous sumac extract exhibited high antibacterial activity against these bacteria (Dahham et al. 2015). Therefore, it appears that the aqueous sumac extract is a promising candidate for the development of antimicrobial agents, particularly against *S. aureus* bacteria.

Although the precise mechanism underlying the antimicrobial properties of sumac extract and its bioactive components remains incompletely elucidated, it is probable that compounds such as β-caryophyllene, a recognized active constituent of sumac extract, contribute to its antimicrobial efficacy. β-caryophyllene has demonstrated potent antibacterial effects against numerous bacterial strains, with a notable impact on gram-positive bacteria compared to gram-negative bacteria (Ahmadian-Attari et al. 2016). Additionally, other compounds like gallic acid, another established active ingredient in sumac extract, also play a role in its antimicrobial activity (Borges et al. 2013). Research suggests that gallic acid may induce irreversible alterations in membrane properties by modifying hydrophobicity, reducing surface negative charge, and causing local rupture or pore formation in bacterial cells, ultimately resulting in the release of essential substances and intracellular components (Mazzara et al. 2023; Oladele et al. 2022).

Another bioactive compound found in sumac, 1,2-dioxo-6-hydroxycyclohexadiene-4-carboxylic acid, belongs to the quinone class. These compounds serve as a source of stable free radicals and can create irreversible complexes with nucleophilic amino acids in proteins. This interaction often results in the loss of protein function and subsequent cell death. Quinone oxidation is likely to target surface-exposed adhesins, cell wall polypeptides, and membrane-bound enzymes (Shabana et al. 2011).

The outcomes of the in vivo investigation revealed that the administration of sumac extract mitigated the symptoms associated with *S. aureus* infection, including weight loss, the formation of wounds, and reduced activity, to a greater extent than the administration of antibiotics. The observed effects are likely attributable, in part, to the antimicrobial bioactive compounds present in sumac extract, as well as to the immune-enhancing properties of sumac extract that enhance the host's immune system (Kossah et al. 2013). This combined action appears to be effective in combatting *S. aureus* bacterial infections in the murine system.

The evaluation of free radical scavenging activity in the aqueous extract of *R. typhina* fruit, as determined through the DPPH method, revealed a direct relationship between the extract concentration and its ability to scavenge DPPH free radicals. Notably, at concentrations ranging from 200 to 1000 mg/ml, the aqueous extract exhibited superior antioxidant activity compared to the control, ascorbic acid. The antioxidant properties of alcoholic extract derived from Chinese sumac fruit, reported remarkable antioxidant attributes at lower concentrations than those employed in the present study. For example, significantly heightened antioxidant properties were observed at a concentration of 0.5 mg/L of sumac alcoholic extract, surpassing those of ascorbic acid [38]. In another study, maximum antioxidant properties were observed at a concentration of 0.038 mg/L of the alcoholic extract of Sumac Suri (Kossah et al. 2010). This discrepancy in findings suggests that the species of sumac and the type of extract used may contribute to the observed variations.

Numerous studies on plant extracts and essential oils have indicated that the presence of flavonoid compounds within them is closely associated with robust antioxidant activity. Some researchers have proposed that the antioxidant and radical scavenging activities of Syrian sumac fruit extract may be attributed to its substantial polyphenol content (Wojtyczka et al. 2014). Furthermore, it's worth noting that the specific chemical composition of essential oils and plant extracts, along with the extraction techniques employed and the assessment methodologies used to determine antioxidant properties, can significantly influence research outcomes (Kasote et al. 2015). Previous studies on essential oils and plant extracts have emphasized the importance of hydrogen-donating

bioactive compounds, including polyphenols, flavonoids, and monoterpenes, in conferring antioxidant properties (Batiha et al. 2022). Hence, it is conceivable that a significant portion of the observed antioxidant properties in sumac aqueous extract can be attributed to the presence of such bioactive compounds.

The findings of this investigation indicated that sumac extract exhibited a moderate to high level of antioxidant activity. Moreover, this extract demonstrated the capability to enhance bacterial susceptibility and reduce biofilm formation among clinical isolates of methicillin-resistant *S. aureus*, thus underscoring its robust antimicrobial potential.

In the in vivo assessments, the administration of sumac aqueous extract ameliorated the symptoms associated with *S. aureus* infection and led to a decrease in the bacterial load in the bloodstream. Remarkably, this effect surpassed that of the antibiotic control group. These findings collectively suggest that the application of sumac aqueous extract, attributed to its rich repository of bioactive compounds, holds substantial promise in addressing antibiotic-resistant *S. aureus* strains, particularly those resistant to methicillin. Consequently, in the development of novel therapeutic modalities for managing chronic and recalcitrant *S. aureus* infections and in mitigating the burgeoning public health challenge posed by the proliferation of such infections, due consideration should be given to the utilization of sumac bioactive compounds that inhibit the growth and propagation of these resilient microorganisms. This avenue of research holds potential for enhancing the precision and efficacy of future treatment strategies.

Abbreviations

MRSA	Methicillin-resistant *Staphylococcus aureus*
DPPH	2,2-Diphenyl-1-picrylhydrazyl
MIC	Minimum inhibitory concentration
AMR	Antimicrobial resistance
HGT	Horizontal gene transfer
WHO	World Health Organization
PPL	Priority pathogen list
GC	Gas chromatograph
MS	Mass spectrometer
IC50	Half-maximal inhibitory concentration
BHA	Butylated hydroxyanisole
BHT	Butylated hydroxytoluene
TSB	Tryptic soy broth
CLSI	Clinical and laboratory standards institute
PBS	Phosphate buffer saline
SD	Standard deviation
UV	Ultraviolet
NA	Nutrient agar
MSA	Mannitol salt agar
ATCC	American type culture collection
NUM	Number
Eps	Efflux pump systems

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13568-024-01759-4.

Supplementary Material 1

Acknowledgements

We are grateful to the North of Tehran Branch, Islamic Azad University for offering the location for our experiments and providing administrative support.

Author contributions

Nafiseh Farazandehnia: Writing– original draft; Writing– review & editing; Visualization; Validation; Resources; Methodology; Data curation. Farzaneh Sotoudegan: Methodology; Validation; Writing– review & editing; Formal analysis; Resources; Conceptualization. Abbas Akhavan Sepahy: Writing– review & editing; Conceptualization; Funding acquisition; Investigation; Supervision; Project administration; Data curation. Mohamad Reza Fazeli: Writing– review & editing; Conceptualization; Data curation; Funding acquisition; Investigation; Validation; Resources; Supervision; Project administration; Methodology; Investigation.

Funding

There are no funders to report for this submission.

Data availability

Data generated or analyzed during this study are included in this published article. However, the data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

I, Mohamad Reza Fazeli, hereby grant permission for the publication of the manuscript titled [Antibacterial and Antioxidant Properties of Sumac Aqueous Extract on Methicillin-Resistant Staphylococcus Aureus: In Vitro and In Vivo Studies], authored by Nafiseh Farazandehnia, Farzaneh Sotoudegan, Abbas Akhavan Sepahy and Mohamad Reza Fazeli in the journal Heliyon. I confirm that I have the necessary rights to grant this permission.

Competing interests

The authors declare that they have no competing interests.

Received: 23 February 2024 / Accepted: 27 August 2024
Published online: 03 October 2024

References

Acharya T (2018) E-TEST (Epsilometer test): Principle, purpose, procedure, results and interpretations. Diakses Pada Tanggal. 1

Adwan G, Abu-Shanab B, Abu-Safiya DI, Abu-Shanab M (2015) Antibacterial activity of *Rhus coriaria.* L. extracts growing in Palestine. IUG J Nat Studies13.

Ahmadian-Attari MM, Amini M, Farsam H, Amin G, Fazeli MR, Esfahani HR, Jamalifar H (2016) Bairami A. isolation of major active antibacterial compounds of sumac fruit (*Rhus coriaria* L.). Int J Enteric Pathogens 4(18):1–5

Ahmadian-Attari MM, Khanlarbeik M, Fazeli MR, Jamalifar H (2017) Sumac (*Rhus coriaria* L.) represents a considerable antibacterial activity against meticillin susceptible and meticillin resistant *Staphylococcus aureus*. Int J Enteric Pathogens 5(10):76–79

Akrayi HF, Abdullrahman ZF (2013) Screening in vitro and in vivo the antibacterial activity of *Rhus coriaria* extract against *S. Aureus*. IJRRAS 15(14):390–397

Álvarez-Martínez FJ, Barrajón-Catalán E, Micol V (2020) Tackling antibiotic resistance with compounds of natural origin: a comprehensive review. Biomedicines 8(12):405

Arabestani MR, Abdoli Kahrizi M (2016) Determining the Agar gene variety (accessory gene regulator) in susceptible and methicillin-resistant *Staphylococcus aureus* strains in clinical samples and carriers employed in remedial centers. J Arak Univ Med Sci 18(11):44–53

Arabestani MR, Rastiany S, Mousavi SF, Ghafel S, Alikhani MY (2015) Identification of toxic shock syndrome and exfoliative toxin genes of *Staphylococcus aureus* in carrier persons, resistant and susceptible methicillin. Tehran Univ Med J 73(25):554–560

Arena K, Trovato E, Cacciola F, Spagnuolo L, Pannucci E, Guarnaccia P, Santi L, Dugo P, Mondello L, Dugo L (2022) Phytochemical characterization of *Rhus coriaria* L. extracts by headspace solid-phase micro extraction gas chromatography, comprehensive two-dimensional liquid chromatography, and antioxidant activity evaluation. Molecules 27(5):1727

Batiha GE, Ogunyemi OM, Shaheen HM, Kutu FR, Olaiya CO, Sabatier JM, De Waard M (2022) *Rhus coriaria* L. (Sumac), a versatile and resourceful food spice with cornucopia of polyphenols. Molecule 27(20):5179

Borges A, Ferreira C, Saavedra MJ, Simões M (2013) Antibacterial activity and mode of action of ferulic and gallic acids against pathogenic bacteria. Microb drug Resist 19(27):256–265

Brooun A, Liu S, Lewis K (2000) A dose-response study of antibiotic resistance in *Pseudomonas aeruginosa* biofilms. Antimicrob Agents Chemother 44(28):640–646

Calcaterra A, D'Acquarica I (2018) The market of chiral drugs: chiral switches versus de novo enantiomerically pure compounds. J Pharm Biomed Anal 147(3):323–340

Carr C, Smith A, Marturano M, Hakki L, Friedman J, Guidry C, McGrew P, McGinness C, Duchesne J, Schroll R (2019) Ventilator-associated pneumonia: how do the different criteria for diagnosis match up? Am Surg 85(1):992–997

Dahham SS, Tabana YM, Iqbal MA, Ahamed MB, Ezzat MO, Majid AS, Majid AM (2015) The anticancer, antioxidant and antimicrobial properties of the sesquiterpene β-caryophyllene from the essential oil of Aquilaria crassna. Molecules 20(20):11808–11829

Dibah S, Arzanlou M, Jannati E, Shapouri R (2014) Prevalence and antimicrobial resistance pattern of methicillin resistant *Staphylococcus aureus* (MRSA) strains isolated from clinical specimens in Ardabil, Iran. Iran J Microbiol 6(3):163–168

Fazeli MR, Amin G, Attari MM, Ashtiani H, Jamalifar H, Samadi N (2007) Antimicrobial activities of Iranian sumac and avishan-e shirazi (*Zataria multiflora*) against some food-borne bacteria. Food Control 18(36):646–649

Ghane M, Babaeekhou L, Shams M (2022) Antimicrobial activity of *Rhus Coriaria* L. and *Salvia Urmiensis Bunge* against some food-borne pathogens and identification of active components using molecular networking and docking analyses. Food Sci Technol 42(9):08221

Giedraitienė A, Vitkauskienė A, Naginienė R, Pavilonis A (2011) Antibiotic resistance mechanisms of clinically important bacteria. Medicina 47(5):19

Gündoğan N, Citak SU, Turan E (2006) Slime production, DNase activity and antibiotic resistance of *Staphylococcus aureus* isolated from raw milk, pasteurised milk and ice cream samples. Food Control 17(43):389–392

Gupta R, Sharma S (2020) Herbal antibiotics: a review. Bull Env Pharmacol Life Sci 9(4):136–142

Ignaciuk A, Vöhringer F, Ruijs A, van Ierland EC (2006) Competition between biomass and food production in the presence of energy policies: a partial equilibrium analysis. Energy Policy 34(23):1127–1138

Kasote DM, Katyare SS, Hegde MV, Bae H (2015) Significance of antioxidant potential of plants and its relevance to therapeutic applications. Int J Biol Sci 11(23):982

Kossah R, Nsabimana C, Zhang H, Chen W (2010) Optimization of extraction of polyphenols from Syrian sumac (*Rhus coriaria* L.) and Chinese sumac (*Rhus typhina* L.) fruits. Res J Phytochem 4(10):146–153

Kossah R, Nsabimana C, Zhang H, Chen W (2013) Evaluation of antimicrobial and antioxidant activities of Syrian Sumac fruit extract. J Nat Prod 6:96–102

Kumar B, Sharma D, Sharma P, Katoch VM, Venkatesan K, Bisht D (2013) Proteomic analysis of Mycobacterium tuberculosis isolates resistant to kanamycin and amikacin. J Proteom 94(6):68–77

Lata M, Sharma D, Deo N, Tiwari PK, Bisht D, Venkatesan K (2015) Proteomic analysis of ofloxacin-mono resistant *Mycobacterium tuberculosis* isolates. J Proteom 127(18):114–121

Li Y, Xiao P, Wang Y, Hao Y (2020) Mechanisms and control measures of mature biofilm resistance to antimicrobial agents in the clinical context. ACS Omega 5(9):22684–22690

Mazzara E, Caprodossi A, Mustafa AM, Maggi F, Caprioli G (2023) Phytochemical investigation of Sumac (*Rhus coriaria* L.) fruits from different Sicilian accessions. Foods 12(34):4359

Nasar-Abbas SM, Halkman AK (2004) Antimicrobial effect of water extract of sumac (*Rhus coriaria* L.) on the growth of some food borne bacteria including pathogens. Int J Food Microbiol 97(38):63–69

Nouwen JL, Ott A, Kluytmans-Vandenbergh MF, Boelens HA, Hofman A, Van Belkum A, Verbrugh HA (2004) Predicting the *Staphylococcus aureus* nasal carrier state: derivation and validation of a culture rule. Clin Infect Dis 39(3):806–811

Oladele OT, Aladejana MO, Adewole TS, Olowookere BD, Oladele JO (2022) Phytochemicals as antimicrobial agents: applications in infectious diseases. In: Handbook of research on advanced phytochemicals and plant-based drug discovery. IGI Global, pp 211–245

Özcan M (2003) Antioxidant activities of Rosemary, sage, and sumac extracts and their combinations on stability of natural peanut oil. J Med Food 6(24):267–270

Pendleton JN, Gorman SP, Gilmore BF (2013) Clinical relevance of the ESKAPE pathogens. Expert Rev Anti-Infect Ther 11(15):297–308

Rhayour K, Bouchikhi T, Tantaoui-Elaraki A, Sendide K, Remmal A (2002) The mechanism of bactericidal action of oregano and clove essential oils and of their phenolic major components on *Escherichia coli* and *Bacillus subtilis*. J Essent Oil Res 15(5):356–362

Shabana MM, El Sayed AM, Yousif MF, El Sayed AM, Sleem AA (2011) Bioactive constituents from *Harpephyllum caffrum Bernh*. and *Rhus coriaria* L. Pharmacognosy magazine 298

Shrivastava SR, Shrivastava PS, Ramasamy J (2018) World health organization releases global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. J Med Soc 32(51):76–77

Skariyachan S, Sridhar VS, Packirisamy S, Kumargowda ST, Challapilli SB (2018) Recent perspectives on the molecular basis of biofilm formation by *Pseudomonas aeruginosa* and approaches for treatment and biofilm dispersal. Folia Microbiol 63(15):413–432

Tabaei S, Kouhi Noghondar M, Mohammadzadeh M, Ataei L, Amel Jamehdar S (2016) Pattern of antibiotic resistance in methicillin-resistant *Staphylococcus aureus* (MRSA) strains isolated from clinical specimens: Imam Reza hospital in Mashhad. Med J Mashhad Univ Med Sci 59(3):64–70

Tendolkar PM, Baghdayan AS, Gilmore MS, Shankar N (2004) Enterococcal surface protein, Esp, enhances biofilm formation by *Enterococcus faecalis*. Infect Immun 72:6032–6039

Wojtyczka RD, Dziedzic A, Kępa M, Kubina R, Kabała-Dzik A, Mularz T, Idzik D (2014) Berberine enhances the antibacterial activity of selected antibiotics against coagulase-negative *Staphylococcus strains* in vitro. Molecules 19(15):6583–6596

Publisher's note