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In Vitro Evaluation of Antimicrobial, Antioxidant, and Cytotoxic Effects of Sumac (Rhus coriaria L.)/Rose Water Mouthwash

Maryam Torshabi[a], **Razieh Shahbazi**[b], **Maryam Nikoosokhan**[c]

[a]Associate Professor, Dept. of Dental Biomaterials, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[b] Laboratory Expert, Dept. of Dental Biomaterials, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[C]Bahar Sepinood Company, Tehran University Science and Technology Park, College of Agriculture, Alborz, Iran.
Correspondence to Maryam Torshabi (Email: torshabi@sbmu.ac.ir).
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Objectives Mouthwashes are one of the most effective non-mechanical methods for removing bacteria from the mouth. This study aimed to assess the cytocompatibility, antimicrobial effects (compared to chlorhexidine mouthwash), and antioxidant activity of an experimental herbal mouthwash made from sumac (Rhus coriaria L.) and rose water.
Methods The sensitivity of Streptococcus mutans, S. sanguinis, Staphylococcus aureus, Candida albicans, and Aggregatibacter actinomycetemcomitans to the experimental mouthwash was estimated by measuring the diameter of the inhibition zones. Additionally, the minimum inhibitory concentrations (MICs) were determined using the redox dye resazurin, as well as the minimum bactericidal/fungicidal concentrations (MBCs/MFCs) using the standard spot inoculation method. Cytotoxicity was evaluated using the methyl thiazolyl tetrazolium (MTT) assay, while antioxidant activity was assessed using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay.
Results The MIC and MBC of the sumac mouthwash for the bacteria under study (except S. mutans) ranged from 0.13 to 16.65 mg/mL. For the yeast C. albicans, the MIC and MFC of the sumac mouthwash were determined to be 0.52 mg/mL. Furthermore, the sumac mouthwash showed no cytotoxicity and demonstrated significant antioxidant effects at various concentrations.
Conclusion Sumac/rose water mouthwash, which is a safe, natural, biocompatible, and antioxidant product, may serve as a viable alternative to chemical antibacterial mouthwashes like chlorhexidine. This is particularly true when it is used in conjunction with regular oral hygiene practices over extended time periods.
Keywords Rhus; Herbal medicine; Mouthwashes; Chlorhexidine; Antioxidants

Introduction

Oral diseases are prevalent non-communicable conditions in humans that can be prevented. Despite significant advancements in oral health globally, many communities still face challenges. The most common chronic infectious disorders in the oral cavity, caused by the production of dental biofilm, include dental caries, gingivitis, and periodontal inflammations. [1]

Halting the progression of oral diseases requires mechanical plaque control (e.g., toothbrushing and flossing) and traditional preventive measures like mouthwash. Mouthwashes or oral rinses serve as safe and cost-effective vehicles for delivering active chemical or natural preventive and therapeutic compounds for oral health. They help eliminate harmful oral bacteria, prevent dental cavities, and significantly reduce plaque formation. Unlike chemical antimicrobial mouthwashes, natural mouthwashes do not contain sugar and alcohol, which can cause xerostomia and potentially induce oral-pharyngeal cancer. Additionally, natural mouthwashes do not disrupt the normal oral flora or cause germ resistance. Moreover, mouthwashes containing natural components offer additional benefits for oral health, such as anti-inflammatory and antioxidant properties. [2-4] Consequently, there is a global demand for the development of natural preventive and therapeutic solutions that can serve as alternatives to effective chemical compounds. These solutions should be capable of simultaneously treating dental caries and periodontal disorders while having minimal side effects. [5]

Chlorhexidine, which is a cationic surfactant with broad-spectrum antibacterial activity and less pronounced antifungal activity, is widely used as a chemical antimicrobial mouthwash in dentistry. However, chlorhexidine comes with certain side effects, including reversible brown staining of teeth, increased formation of calculus, and temporary impairment of taste sensation. [6] It is crucial to explore natural therapies that can replace chlorhexidine and mitigate its harmful effects. For instance, mouthwashes containing herbal extracts have not been shown to cause adverse changes in tooth color or alter oral flavor. Herbal mouthwashes are also preferable to chlorhexidine mouthwashes for long-term use in oral diseases as they help prevent plaque formation and reduce gingival inflammation.

Moreover, certain plant compounds have the ability to inhibit bacterial growth and reduce the likelihood of antibiotic resistance among biofilm bacterial strains. [3, 6] In Persian medicine, various pharmaceutical dosage forms, such as dental powders and mouthwashes, incorporate herbal ingredients with diverse mechanisms of action. These herbal components have been shown to possess antimicrobial, anti-inflammatory, and antioxidant properties. One such herb is sumac (Rhus Coriaria L., Anacardiaceae), which grows abundantly in the wild in Iran. Sumac has been traditionally used in food and herbal

medicine as a popular spice, known for its anti-inflammatory, antibacterial, antioxidant, analgesic, and wound-healing effects. Sumac is rich in vitamins, minerals, flavonoids, anthocyanins, gallic acid, flavones, nitrate, nitrite, organic acids (such as malic acid, citric acid, and tartaric acid), and fatty acids (including palmitic acid, stearic acid, oleic acid, and linoleic acid). Additionally, tannins are a significant component of polar chemicals in sumac extract. [7-12]

Previous studies have documented the impact of sumac on endothelial vessels, showing that it leads to a significant reduction in systolic blood pressure (SBP), diastolic BP (DBP), serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and body mass index (BMI). Oxidative stress can harm the body's endothelium by promoting vascular dilation, smooth muscle hypertrophy, and collagen deposition. Consequently, it can enhance vascular contraction activity. [13, 14] Rhus coriaria, the source plant of sumac, contains natural antioxidants and phenolic compounds like tannins and flavonoids. Thus, treatment with this plant extract can effectively inhibit vascular endothelial damage caused by free radicals. Additionally, due to its more potent antioxidant activity compared to butylated hydroxytoluene (BHT), this extract can serve as a natural antioxidant supplement in food. [13]

For centuries, Iranians have recognized the medicinal benefits of sumac and rose water, the main product of Rosa damascena. These ingredients have been used alone or in combination with other herbs to prevent caries and treat benign, non-contagious mouth ulcers. [15] Rose water has been reported to possess antimicrobial effects, inhibiting 50% of Candida albicans growth. [16, 17] Sumac fruit extracts have demonstrated remarkable antioxidant properties in combating lipid peroxidation and scavenging free radicals. [12] Additionally, our previous study found that water extracts of R. coriaria L. fruit effectively inhibit the expression of glycosyltransferase genes involved in biofilm formation in Streptococcus mutans. [18] Considering the significant biological effects of sumac, this study aimed to investigate the antibacterial/antioxidant efficacy and cytotoxicity of an experimental sumac/rose water mouthwash.

Methods and Materials

Mouthwash Preparation

The maceration process was used to prepare the sumac mouthwash. A total of 8 g of crushed Iranian sumac peel fruit was combined with 240 mL of pure rose water and left to incubate overnight at room temperature. After filtering, a preservative, sodium benzoate, was added to the mixture.

Microbial Strains and Inoculum Preparations

The bacterial strains used in this study consisted of three gram-positive strains (S. mutans ATCC 35668, S. sanguinis ATCC 10556, and S. aureus ATCC 6538), one gram-negative strain (Aggregatibacter actinomycetemcomitans ATCC 700685), and one opportunistic pathogenic yeast strain (C. albicans ATCC 10231). The inoculum was prepared by direct saline suspension of isolated bacterial colonies selected from an overnight brain heart infusion (BHI; Conda, Spain) agar culture. The suspension was adjusted to achieve a turbidity equivalent to a 0.5 McFarland turbidity standard, corresponding to 1.5×10^8 colony-forming units (CFU)/ mL. [19]

Agar Dilution Method Assays

The antibacterial activity of sumac and chlorhexidine (0.2%, Najo-Pharmaceutical Co., Iran) mouthwashes was determined using the agar well diffusion assay. [20] With a sterile swab that was moistened with the bacterial suspension, an inoculum comprising 10^6 CFU/mL of each bacterial culture was dispersed on nutrient agar plates. Subsequently, wells with a diameter of 5 mm were created in the agar medium, and 50 µL of sumac mouthwash (33.3 mg/mL), chlorhexidine mouthwash (2 mg/mL), or rose water (as a negative control) were added to the respective wells (triplicate; 3 independent tests; n = 9). The plates containing S. sanguinis, S. aureus, and C. albicans were incubated aerobically at 37 °C for 24 hours, while A. actinomycetemcomitans and S. mutans were incubated anaerobically at 37 °C for 72 and 48 hours, respectively. The zones of growth inhibition were measured in millimeters after the respective incubation times.

Determination of Minimum Inhibitory and Bactericidal/Fungicidal Concentration

Following the guidelines of the Clinical and Laboratory Standards Institute, the minimum inhibitory concentrations (MICs) were determined in sterile 96-well microplates using the broth microdilution method. Overnight cultures of the bacteria were diluted to achieve a suspension equivalent to 10^6 CFU/mL. Serial two-fold dilutions of the sumac/rose water and chlorhexidine mouthwashes were prepared in the BHI broth medium (triplicate; three independent tests; n = 9). Subsequently, the suspension of each organism was inoculated into the wells, except for the negative control. The microplates were incubated at 37 °C for 24 hours, except for A. actinomycetemcomitans, which was incubated under anaerobic conditions at 37 °C for 48 hours. The lowest concentration that inhibited the growth of the microorganisms was recorded as the MIC. Negative controls (mouthwash + BHI) and positive controls (microorganism + BHI) were also included in the experiment. After incubation, all wells were treated with blue resazurin dye (Sigma, Germany) at a concentration of 0.01% (20 L per well). Color changes indicative of growth

(turning purple) were observed after two hours of incubation, and the lowest concentration without any color change (remaining blue) was determined as the MIC. To determine the minimum bactericidal/fungicidal concentration (MBC/MFC), 5 µL of microbial suspension from each well (3 replicates) with the highest MIC concentrations and the lowest MIC concentration were plated on BHI agar plates (triplicate; 3 independent tests; n = 9). The plates were then incubated at 37 °C for 24 hours (for all microorganisms studied except A. actinomycetemcomitans) and 72 hours (for A. actinomycetemcomitans). The MBC/MFC was defined as the lowest concentration that showed no visible microbial growth (no microbial colonies). [19, 20]

Cytotoxicity Evaluation

In this study, the cytotoxicity of sumac/rose water mouthwash and its effect on the viability and proliferation of human gingival fibroblasts (HGF1 PI 1, NCBI: C165) were evaluated using the methyl thiazolyl tetrazolium (MTT) test, following the ISO-10993-5 standard, and compared to chlorhexidine mouthwash.

Briefly, 5,000 cells in the logarithmic growth phase were cultured in each well of a 96-well cell culture plate using DMEM cell culture medium (Gibco, UK) supplemented with FBS serum and penicillin-streptomycin antibiotics (Gibco, UK). After 24 hours of incubation at 37 °C, 98% humidity, and 5% CO_2, the HGF cells were treated with different concentrations (0-75% v/v) of sumac/rose water mouthwash, as well as the mouthwash solvent (rose water) as the control group.

At 24 and 72 hours after treatment, the culture medium in each well was replaced with a medium containing 10% MTT dye (Sigma, Germany). After two hours of incubation and the formation of formazan crystals, the MTT dye was replaced with DMSO solvent to dissolve the crystals. The optical density of the resulting colored solutions was measured using a microplate reader (Anthous 2002, Austria) at wavelengths of 570 and 620 nm, and the percentage of cell viability was calculated.

The experiments were performed in triplicate and repeated for three times, yielding similar results (n = 9).

Antioxidant Activity Evaluation

In this study, the antioxidant effect of sumac/rose water mouthwash was investigated using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) test, with vitamin C (ascorbic acid) serving as the positive control group.

Different concentrations (ranging from 0.01% to 50% v/v) of the sumac/rose water mouthwash were prepared. Each concentration was mixed with 1 mL of 0.1mM DPPH solution (Sigma, Germany). A blank solution consisting of DPPH solution and deionized water was also prepared. The resulting solutions were incubated in the dark at room temperature for 30 minutes.

Following incubation, the optical density of the solutions was read at a wavelength of 517 nm using a spectrophotometer. The percentage of DPPH free radical inhibition was calculated.

The experiments were conducted in triplicate and repeated for three times, yielding similar results (n = 9).

Statistical Analysis

The data were presented as mean ± SD from at least three independent experiments (n = 9; normal distribution). Statistical analysis of the MTT assay results was performed using GraphPad Prism version 9.0.0. One-way ANOVA was conducted, followed by the Tukey post hoc test for pairwise comparisons, with a significance level set at 0.05.

Results

Antimicrobial Activity Evaluation

The well-diffusion agar method was used to investigate the preliminary antibacterial activity of sumac and chlorhexidine mouthwashes. The inhibition zones surrounding the wells were measured to assess the antibacterial effect. In this study, all microorganisms tested, except for S. mutans, showed an antibacterial effect of the sumac mouthwash. However, the chlorhexidine mouthwash exhibited superior antibacterial action against all tested microorganisms (Table 1). The MIC and MBC of the chlorhexidine mouthwash were determined to be 0.001 mg/mL, indicating its highest antibacterial activity against S. mutans. The differences between the two mouthwashes were significant, and the negative control, rose water, did not exhibit any antibacterial effect.

Table1: Zone of inhibition (ZOI), Minimum inhibitory concentration (MIC), Minimum bactericidal concentration (MBC), and minimum fungicidal concentration (MFC) of Sumac/Rose water and chlorhexidine mouthwashes

	Chlorhexidine mouthwash (2 mg/mL)			**Sumac/Rose water mouthwash (33.3 mg/mL)**		
	ZOI in mm (Mean± SD)	MIC (mg/mL)	MBC (mg/mL)	ZOI in mm (Mean± SD)	MIC (mg/mL)	MBC (mg/mL)
Streptococcus mutans	36.5 ± 0.71	0.001	0.001	-	-	-
Streptococcus sanguinis	36 ± 1.41	0.002	0.004	18.5 ± 0.71	0.13	0.13
Staphylococcus aureus	30 ± 0.0	0.001	0.002	15 ± 0.0	2.08	16.65
Aggregatibacter actinomycetemcomitans	46.5 ± 2.1	0.002	0.03	16 ± 0.0	8.33	16.65
	ZOI in mm (Mean± SD)	MIC (mg/mL)	MBC (mg/mL)	ZOI in mm (Mean± SD)	MIC (mg/mL)	MFC (mg/mL)
Candida albicans	29 ± 0.0	0.008	0.008	15.5 ± 0.71	0.52	0.52

Cytotoxicity Evaluation

According to Figure 1, no cytotoxicity (viability reduction below 70%) was observed at any of the tested concentrations of the sumac/rose water mouthwash and rose water after 24 and 72 hours of exposure to HGF cells. The percentage of cell viability for concentrations ranging from 1% to 50% (v/v) was similar to that of the negative control group and was about 100%, indicating no cytotoxicity and approximately 100% cell viability ($p > 0.05$). However, there was a statistically significant reduction in cell viability of approximately 20%-30% at the concentration of 75% (v/v) compared to the negative control group ($p < 0.05$).

In contrast, all concentrations of the chlorhexidine mouthwash exhibited statistically significant cytotoxicity, with a decrease in cell viability ranging from approximately 70% to 95% ($p < 0.05$).

Antioxidant Activity Evaluation

According to Figure 2, the antioxidant activity of the sumac/rose water mouthwash (DPPH free radical inhibition) was comparable to that of ascorbic acid (vitamin C), which served as the positive control. The antioxidant activity remained at approximately 100% for concentrations ranging from 1% to 50% (v/v). At very low concentrations (0.01% and 0.1% v/v), a free radical inhibition of approximately 30% to 60% was observed.

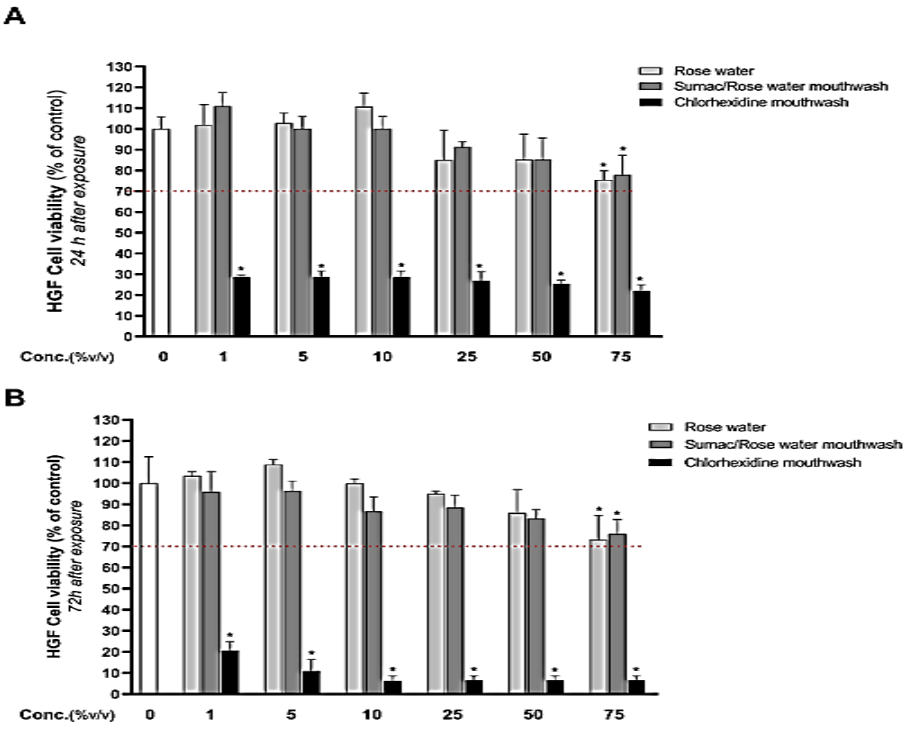

Figure 1: The effect of different concentrations [0-75% (v/v)] of Rose water, Sumac/Rose water mouthwash, and

Chlorhexidine mouthwash on the viability, proliferation, and cytotoxicity of HGF cells at 24 and 72 hours after exposure using the quantitative MTT assay. Stars on the columns indicate a statistically significant difference ($p<0.05$) compared to the control group (without treatment).

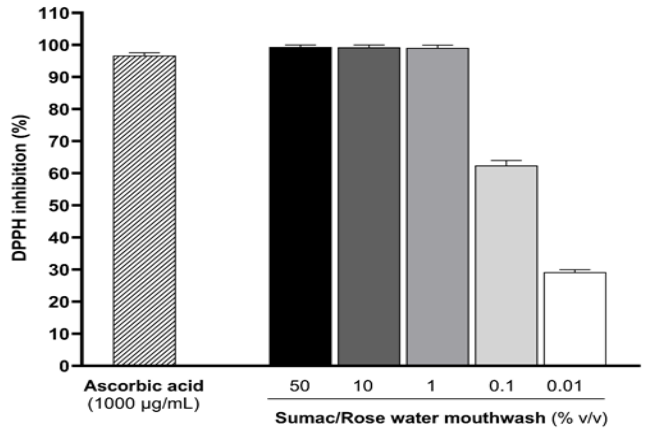

Figure 2: The effect of different concentrations [0.01-50% (v/v)] of Sumac/Rose water mouthwash on the inhibition of DPPH free radicals compared to the positive control (vitamin C).

Discussion

Plaque, a biofilm consisting of various microbial populations, is the underlying cause of serious dental issues such as caries and periodontal disease. In dentistry, medicinal herbs have been effectively used for their antioxidant, antiseptic, and analgesic properties. Herbal mouthwashes, derived from natural plant extracts, including leaves, fruits, seeds, and tree oils, have gained popularity over chemical mouthwashes due to their non-irritating, non-staining, and alcohol-free nature. They pose minimal risks and exhibit minimal if any, side effects. [21] While chlorhexidine is currently considered the standard antimicrobial mouthwash, there is a growing trend toward the use of medicinal herbs with antimicrobial properties and few adverse effects for the control, prevention, and treatment of oral issues such as tooth decay, periodontal disease, and oral ulcers.

In this study, chlorhexidine mouthwash demonstrated significantly greater efficacy than sumac mouthwash against all four studied microorganisms. However, it is important to note that chlorhexidine mouthwash has several adverse effects, including teeth stains, alterations in taste perception, inflammation, and dryness of the mouth, despite its effectiveness against a wide range of microorganisms. [22] On the other hand, sumac/rose water mouthwash exhibited a lower but still noteworthy antibacterial activity compared to chlorhexidine mouthwash. Sumac is commonly used as a condiment in the food industry, and while there have been limited studies on its antimicrobial effects on oral microorganisms, most research has focused on its effects on food-related bacteria. [23] Rose water (R. damascena) was incorporated as a solvent base in the sumac mouthwash due to its antioxidant and anti-inflammatory properties. While some studies have reported the antibacterial properties of rose water [16], the present study indicated otherwise.

Previous studies have indicated that sumac extract exhibits a stronger effect against gram-positive bacteria compared to gram-negative bacteria. In a previous study by Othman et al. (2019), the effect of R. coriaria L. (a Syrian sumac plant) was investigated on gram-negative bacteria (with MICs ranging from 1 to 3.5 mg/mL) and gram-positive bacteria (with MICs ranging from 0.5 to 1.5 mg/mL). The findings demonstrated that sumac mouthwash significantly affected periodontal gram-negative bacteria, such as A. actinomycetemcomitans, as well as gram-positive bacteria like S. aureus. [24] Similarly, Mahdavi et al. (2018) reported the sensitivity of S. aureus to sumac, which is consistent with the findings of the present investigation. [24] In 2016, Vahid-Dastjerdi et al. discovered that sumac water extract inhibited biofilm formation in S. mutans by reducing the expression of gtfB, C, and D genes. [18] In the present study, sumac mouthwash was effective against S. sanguinis, with MIC and MBC values of 0.13 mg/mL but did not demonstrate any antibacterial effect against S. mutans.

Candidiasis is an opportunistic infection caused by Candida species as a result of compromised host defense. Challenges in treating fungal diseases, including drug resistance and side effects, have prompted researchers to explore the development of new drugs, particularly herbal extracts. [25] In 2019, Behzadi-Rad et al. discovered that the anti-Candida methanolic extract of R. coriaria exhibited greater efficacy against C. albicans compared to both aqueous and ethanol extracts. [26] The findings of the present study provide valuable insights into the anti-Candida action of sumac mouthwash, with a reported MIC of 0.52 mg/mL, as previously reported by Pirbalouti et al. in 2009. [25]

Moreover, sumac extract has demonstrated the ability to inhibit alveolar bone loss through its antioxidant properties. It can serve as an alternative to non-steroidal anti-inflammatory drugs (NSAIDs) to reduce and prevent periodontal diseases. [27] In this study, sumac mouthwash exhibited a growth inhibition effect against A. actinomycetemcomitans, with an MIC of 8.32 mg/mL and a bactericidal effect with an MBC of 16.65 mg/mL.

This study aimed to investigate the antioxidant activity of different concentrations of sumac/rose water mouthwash. The results revealed that the antioxidant activity increased in a concentration-dependent manner. However, the difference in antioxidant activity at higher concentrations was not statistically significant.

The findings of this research align with a study by Fereydoun Far et al. (2019), which also highlighted the strong antioxidant activity of Iranian sumac [28]. They observed a direct correlation between the flavonoid and tannin content of Iranian sumac and its antioxidant capacity. Kosar et al. (2007) examined the methanolic extract of sumac and found it to be rich in anthocyanins and hydrolyzable tannins, with gallic acid as the main phenolic compound. According to their findings, sumac extract exhibited potent antioxidant effects, with an effective scavenging concentration (EC50) of 0.70 µg/mL in both the tannin and ethyl acetate fractions and 5.33 µg/mL in the anthocyanin-rich fraction. They concluded that hydrolyzable tannins were primarily responsible for the antioxidant activity of sumac. [29] Tannins, which constitute a significant portion of phenolic compounds, exhibit antibacterial effects by inhibiting extracellular microbial enzymes, metal ion complexation, and/or substrate deprivation. Another study attributed the antibacterial action of sumac to its high levels of citric and malic acid. [7, 8] Sumac contains gallic acid as one of its active components. When gallic acid is used against bacteria, it induces changes in hydrophobicity, reduces negative surface charge, and may lead to the formation of pores in the cell membrane. These effects contribute to the leakage of intracellular material. Previous research has demonstrated the antibacterial properties of gallic acid, a component of the sumac plant, against Porphyromonas gingivalis and A. actinomycetemcomitans. Another active component found in sumac is the quinone 1,2-dioxo-6-hydroxycyclohexadine-4-carboxylic acid. These substances constantly generate free radicals, which can form stable compounds with the nucleophilic amino acids of proteins. This, in turn, leads to the loss of their functionality and eventual cell death. Quinone oxidation specifically targets surface-exposed adhesins, cell wall polypeptides, and membrane-bound enzymes. Therefore, sumac extract is likely to exert its effects against these microbes by modifying the characteristics of their cell walls. [30-32]

Human gingival fibroblasts are a crucial cellular component of gingival tissue and possess characteristics similar to embryonic cells, including self-renewal and clonogenicity. [33] Fortunately, in this study, no cytotoxic effects were observed on HGF cells following the use of sumac/rose water mouthwash. While there is a lack of comparable investigations on the effect of sumac, specifically on HGF cells, studies have shown that sumac exhibits time- and concentration-dependent cytotoxic effects on cancer cells. [34-36]

Conclusion

Herbal products have shown remarkable efficacy with minimal adverse effects, making them suitable for long-term use as preventive or therapeutic measures. Within the limitations of the present study, it can be concluded that a natural mouthwash containing components from R. coriaria L. has the potential to serve as a promising natural antimicrobial and antioxidant agent for maintaining oral health. However, further experimental and clinical studies are necessary to validate these findings.

Conflict of Interest

No Conflict of Interest Declared■

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