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Antioxidant and Antimicrobial Capacity of Quinic Acid

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Abstract

Recently, agents with natural antioxidant and antimicrobial properties have been popularly studied. For this purpose, phenolic compounds, terpenes, and organic acids are examined for their antioxidant and antimicrobial properties. Of these, organic acids are increasingly being used in pharmacology, medicine, food, and industry. Quinic acid is a natural organic compound found in many edible fruits and plants. In this study, the antioxidant effect of quinic acid, which has the structure of cyclohexane carboxylic acid, was determined *in vitro* using seven different methods (DPPH, ABTS, CUPRAC, DMPD, FRAP, Fe^{3+} reduction, and Total antioxidant method). In addition, its antimicrobial effect on fungi (C. albicans), gram-positive bacteria (*S. aureus, S. pyogenes*), and gram-negative bacteria (*E. coli, K. pneumoniae, and P. aeruginosa*) were determined by the disk diffusion method. As a result, it was found that quinic acid has broad-spectrum antimicrobial properties, but its antioxidant properties are too low to be highlighted. While its antimicrobial activity was quite good, especially on *K. pneumoniae E. coli, S. aureus, S. Pyogenes*, and *P. aeruginosa*, it did not show any effect on *C. albicans*. Although the antioxidant property of quinic acid is low, it showed more antioxidant properties in the DMPD method, which is one of these methods, because it dissolves very well in water.

1. Introduction

Quinic acid (1, 3, 4, 5-tetrahydroxy cyclohexane carboxylic acid) is a cyclohexanecarboxylic acid found in coffee beans, cinchona bark, potatoes, apples, and peaches [1]–[4]. It has been reported that quinic acid has radioprotective, anti-diabetic, and anti-neuroinflammatory activities and is also an antimutagenic and anti-inflammatory agent [2], [5]–[8]. Quinic acid improves DNA repair and leads to NF-κB inhibition [9]–[11]. In addition, experiments on mice have shown that quinic acid has neuroprotective effects on dementia [12].

Antioxidants are compounds that can scavenge free radicals in the human body [13]. Antioxidants are compounds that can prevent oxidation processes that occur under reactive oxygen species. Because of these properties, they are used to stabilize pharmaceuticals, foodstuffs, petrochemicals, and cosmetics [14]. In addition to antioxidant compounds, research is carried out on what antimicrobial agents are. With these aspects, it finds study area in organic acids found in plants [15].

In this area, revealing the antioxidant and antimicrobial effects of natural products is very important in terms of being economical and yielding efficient results [16]. Therefore, in this study, the antioxidant and antimicrobial effects of quinic acid were investigated.

2. Material and Method

D-Quinic acid, DPPH (2,2 Diphenyl-1-picrylhydrazyl), $FeCl_36H_2O$, NH_4SCN, $FeCl_24H_2O$, $CH_3COONa3H_2O$, Na_2HPO_4, CH_3COONH_4, $CuCl_2$, ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt), DMPD (N,N-Dimethyl-p-phenylenediamine dihydrochloride) are purchased from Sigma Aldrich.

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Tested Microorganisms; *Klebsiella pneumoniae* ATCC 13883, *Pseudomonas aeruginosa* ATCC 9027, *Escherichia coli* ATCC 11229, *Candida albicans* ATCC 10231, *Staphylococcus aure*us ATCC 25923, strains are purchased from Microbiologics. *Streptococcus pyogenes* (ATCC 19615) was obtained from Ankara Refik Saydam Public Health.

250 µM DPPH solution has used the determination of the DPPH radical scavenging activity of quinic acid [17]. DPPH inhibition activities of quinic acid, BHT, BHA, and Trolox were determined at a wavelength of 517 nm in a spectrophotometer. To measure ABTS scavenging activity of quinic acid; 2 ml 2mM ABTS was added to Quinic acid, Trolox, BHT, and BHA solutions from ABTS radical formed by stirring 2 mM ABTS and 2.45 mM $K_2O_8S_2$ and incubated for half an hour. Then the % reduction against the control solution at 734 nm was determined [18], [19]. The cupric ion (Cu^{2+}) reducing capacities of quinic acid and standards were determined by the CUPRAC method. For this, 0.25 ml $CuCl_2$ of 0.01 M, 0.25 ml of $7.5x10^{-3}$M methanolic neocuprine solutions, and 1 M ammonium acetate buffer (pH: 6.5) were transferred to test tubes. After mixing the solution, different concentrations of quinic acid and standards were added. The absorbances were recorded at 450 nm [20]. Quinic acid and standards were taken into test tubes with $NaCH_3COO$ buffer solution with a pH of 3.6 for antioxidant analysis according to the FRAP method. Then, 20 mM $FeCl_3$ solution and FRAP reagent were added. The test tubes were mixed by vortex and their absorbances were recorded at 593 nm [21]. The DMPD radical scavenging activity of quinic acid was performed using the method of Fogliano et al [22]. For this, 0.001 M DMPD· solution was prepared by adding 0.1M DMPD, acetate buffer (pH: 5.3), and 0.05 M $FeCl_3$ solution. Absorbance measurements were made at 505 nm [22]. Fe^{3+}- Fe^{2+} reducing capacity was determined according to the Oyaizu method [23]. Quinic acid and standard solutions prepared at different concentrations were added to test tubes. The mixture formed by adding 0.2 M phosphate tampon (pH: 6.6) and 1 ml 1% $K_3[Fe(CN)_6]$ was incubated at 50°C. After these procedures, 10% (TCA) and 0.1% $FeCl_3$ were added to the reaction mixture, and absorbances were recorded at 700 nm [23]. Total antioxidant activity determination was carried out according to the Ferric Thiocyanate Method [24]. In this method, lipid peroxides formed in linoleic acid emulsion are left to auto-oxidation in the dark at 37°C; It is based on measuring the color change resulting from the reaction with $FeCl_2$ and NH_4SCN solutions at regular intervals at 500 nm [24].

To determine antimicrobial activity, bacteria grown in a liquid medium were first inoculated into a solid medium on sterile discs. Then, the antimicrobial activity of quinic acid was investigated according to the Disk Diffusion method using erythromycin as a positive control [25]. Inhibition zone diameters were measured for *E. coli*, *S. aureus*, *P. aeruginosa*, and *S. pyogenes* bacteria after 24 hours of incubation at 37°C and after 48 hours of incubation at 30°C for *C. albicans*. The same procedure was repeated for the positive (erythromycin 15µg) and negative control (water). Each test was performed in 3 replicates at different times [26].

3. Results and Discussion

According to the results given in Figure 1, it was found that the inhibition capacity of DPPH• of quinic acid is very low.

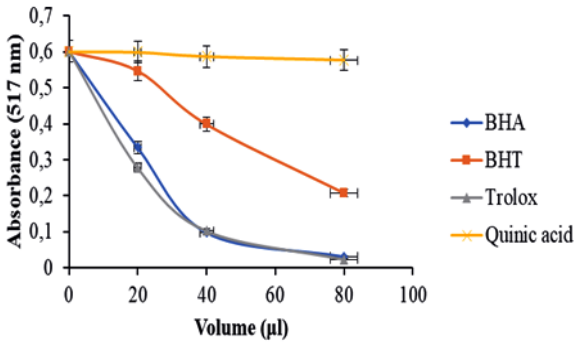

Figure 1. DPPH• radical scavenging activity of quinic acid (30 mg/ml) and standards (at 1mg/ml concentration)

It has been determined that quinic acid does not inhibit ABTS radical as a result of experiments with solutions of quinic acid prepared at concentrations of 1 mg/ml, 30 mg/ml, and 100 mg/ml. $ABTS^{\bullet+}$ scavenging of quinic acid (30mg/ml) and standard antioxidants (at 1 mg/ml concentration) is given in Figure 2.

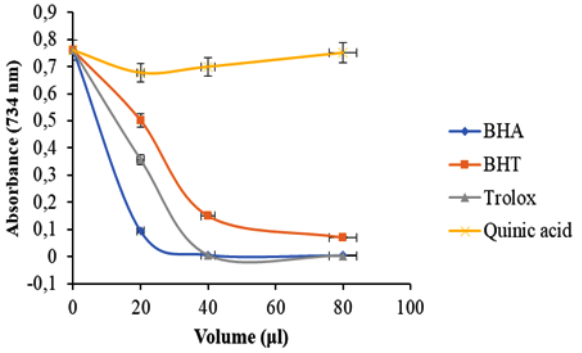

Figure 2. ABTS^{+} radical scavenging activity of quinic acid and standards

DMPD$^{\cdot+}$ inhibition was determined with the solutions of quinic acid prepared at 30 mg/ml concentration, and a decrease was observed in the results, which increased regularly with the increase in concentration (Figure 3). On the other hand, since 30 mg/ml and 100 mg/ml were quite high concentrations, it was observed that quinic acid had a scavenging activity of DMPD$^{\cdot+}$ radical, but this was low.

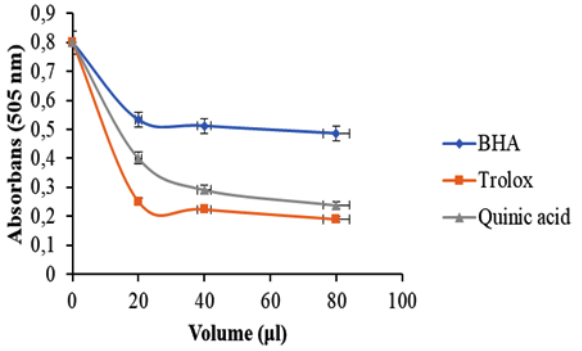

Figure 3. DMPD$^{\cdot+}$ radical scavenging activity of quinic acid and standards

The antioxidant capacities of quinic acid (30 mg/ml), BHT, BHA, and Trolox (at 1 mg/ml concentration) were determined by the CUPRAC method and given in the graph in Figure 4. According to the test results, quinic acid did not show antioxidant properties in the CUPRAC method.

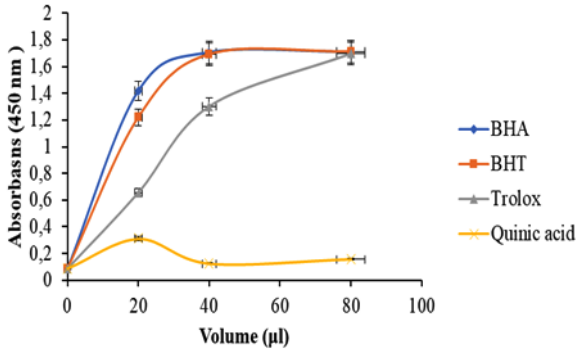

Figure 4. Reducing capacity results of quinic acid and standard antioxidants by the CUPRAC method

In addition, the ferric ion-reducing capacities of 30 mg/ml quinic acid and standard antioxidants (BHA, BHT, and Trolox (at 1 mg/ml concentration)) were compared and shown in Figure 5. As a result of the experiments, the ability of quinic acid to reduce CUPRAC, FRAP, and ferric ions was not observed.

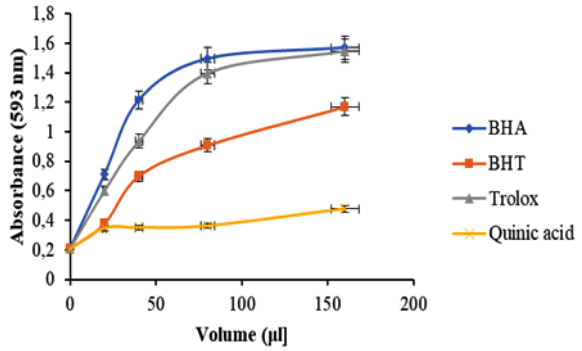

Figure 5. Reducing the capacity of quinic acid and standard antioxidants by the FRAP method

Fe^{3+}- Fe^{2+} reducing activity assay was also performed for quinic acid (30 mg/ml), Trolox, BHA, and BHT (1 mg/ml) the results are given in the graph in figure 6. According to these results, quinic acid did not show antioxidant properties according to the Fe^{3+}-Fe^{2+} reduction method.

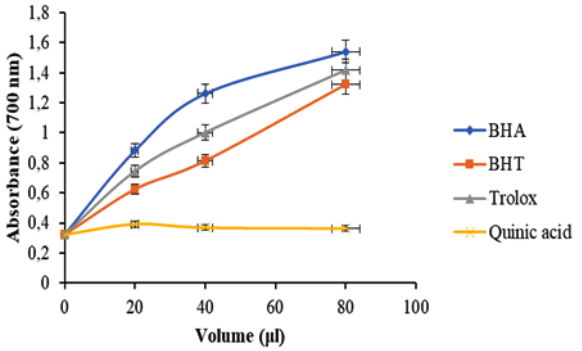

Figure 6. Fe^{3+} Fe^{2+} reduces the capacity of quinic acid and standard antioxidants

Total antioxidant activity determination according to Ferric Thiocyanate Method was also performed in 30 mg/ml concentration quinic acid solution and standards (1mg/ml), and the results are given in the graph in figure 7. The percentages of lipid peroxidation in 80 µl of quinic acid prepared at a concentration of 30 mg/ml at 72 hours and Ferric Thiocyanate lipid peroxidation reduction percentages of the standards, respectively; BHT (99.90%) > BHA (93.93%) > Trolox (80.92%) > quinic acid (44.75%) (Figure 7).

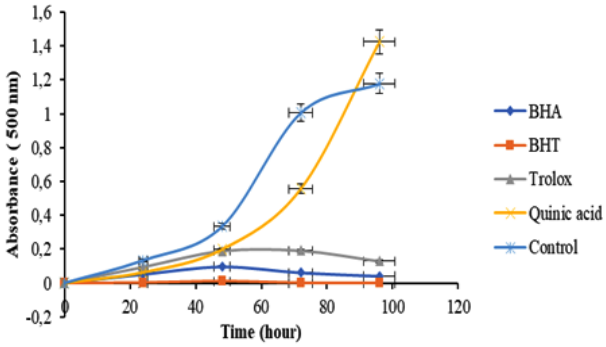

Figure 7. Total antioxidant activity of quinic acid and standard antioxidants

Table 1. Antioxidant activity test results

	IC_{50} (µg/ml)			$A_{0.5}$ (µg/ml)			% Reduction (at 72.hour)
Standards and sample	**DPPH**	**ABTS**	**DMPD**	**CUPRAC**	**FRAP**	**Fe^{3+} reduction**	**Total antioxidant**
BHA	23.07	13.70	83.68	6.35	12.17	5.78	92.82
BHT	63.78	26.79	-	9.60	33.29	12.83	98.10
Trolox	18.79	18.10	18.14	15.33	17.20	8.85	80.62
Quinic acid	-	-	2965	-	-	-	44.75

IC_{50}: Concentration that inhibits 50 percent of the radical, $A_{0.5}$: Concentration at 0.5 nm

The antimicrobial activity of quinic acid was investigated and the results are given in Table 2. Quinic acid was highly effective on gram-negative and gram-positive bacteria, but not on *Candida albicans* (Figure 8). In addition, the % inhibition values of quinic acid according to the erythromycin antibiotic are given in Table 3.

Table 2. Results of antimicrobial activity of quinic acid (mm)

	K. pneumoniae	***E. coli***	***S. aureus***	***S. Pyogenes***	***P. aeruginosa***	***C. albicans***
Quinic acid (100 mg/ml)	16.53±1.48	15.10±0.18	17.57±0.9	16.41±0.7	13.20±1.2	-
Eritromisin (E-15)	16.43±0.02	14.31±1.4	18.97±0.47	20.70±0.0	12.63±0.02	15.19±1.13

Table 3. % Inhibition values of quinic acid compared to erythromycin antibiotic

	% Inhibition					
	K. pneumoniae	***E. coli***	***S. aureus***	***S. Pyogenes***	***P. aeruginosa***	***C. albicans***
Quinic acid (100 mg/ml)	100.6	105.52	92.62	79.27	104.51	-

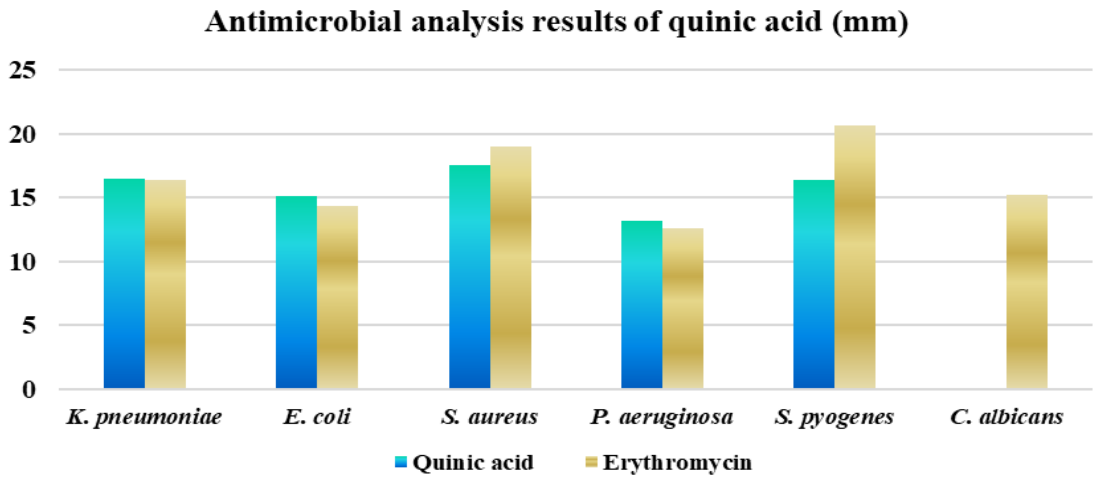

Figure 8. Results of antimicrobial analysis of quinic acid

As a result of the experiments (Table 1), it was found that the inhibition capacity of DPPH$^{\bullet}$ radical is almost non-existent. It also does not inhibit $ABTS^{+\bullet}$ radical which was determined as a result of experiments performed with quinic acid solutions prepared at concentrations of 1 mg/ml, 30 mg/ml, and 100 mg/ml. The $DMPD^{\bullet+}$ radical scavenging activity of quinic acid was determined with quinic acid solutions prepared at 30 mg/ml and 100 mg/ml concentrations, and it gave a reduction result that increased regularly with concentration. The IC_{50} value for the DMPD of quinic acid was found to be 2965 µg/ml. Accordingly, the antioxidant capacity of quinic acid is very low. The reason for the inhibition of the $DMPD^{\bullet+}$ radical of quinic acid in repeated experiments can be shown as its extremely good solubility in water. It was determined that quinic acid did not show antioxidant activity in experiments performed at different concentrations according to the CUPRAC method. It was also observed that quinic acid did not have FRAP-reducing activity at 30 mg/ml and 100 mg/ml concentrations. Fe^{3+}- Fe^{2+} reduction activity test was carried out in quinic acid solutions prepared at different concentrations and standard antioxidants, but according to the results, quinic acid did not show antioxidant properties according to the Fe^{3+} reduction method. In the determination of total antioxidant activity according to the ferric thiocyanate method, the percentage of lipid peroxidation of ferric thiocyanate in 72 hours was determined as 44.75% at a 30 mg/ml concentration of quinic acid. According to the results, it was observed that quinic acid inhibited lipid peroxidation, albeit in a small amount. In the experiments, it was determined that quinic acid, which was mentioned as an antioxidant before, could not be highlighted in terms of antioxidant properties [12], [27]. It has been reported that quinic acid supports the synthesis of tryptophan and nicotinamide, thus increasing serum thiols and showing antioxidant properties [28]. On the other hand, it was previously reported that quinic acid did not show antioxidant properties compared to DPPH, TEAC, and FRAP methods [29]. In this study, the contradiction about whether quinic acid has antioxidant properties has been eliminated and it has been determined that quinic acid cannot be shown as an antioxidant. In addition, studies are showing that phenolic compound derivatives of quinic acid have strong antioxidant properties [30], [31]. However, while these quinic acid derivatives have a phenolic ring, quinic acid is in the cyclohexane structure, which is a more stable chemical structure. Although there are OH groups in the antioxidant compounds in the chemical structure of quinic acid, the absence of the aromatic ring negatively affected its antioxidant properties.

The antimicrobial activity of quinic acid; was examined on gram-positive and gram-negative bacteria and fungi and the results are given in Tables 2 and 3. The antimicrobial activity of quinic acid solution prepared at 100 mg/ml concentration was investigated on *E. coli*, *K. pneumoniae*, *S. aureus*, *P. aeruginosa*, *S. pyogenes*, and *C. albicans*. According to these results, it was observed that quinic acid is highly effective, especially on gram-positive bacteria (*S. aureus*, *S. pyogenes*) and gram-negative bacteria (*P. aeruginosa*, *E. coli*, *K. pneumoniae*). It even inhibited *K. pneumoniae*, *E. coli*, and *P. aeruginosa* bacteria more than the antibiotic erythromycin. On the other hand, no effect of quinic acid on C. albicans was found in triple experiments. In other words, the antifungal effect of quinic acid was not observed. It

has been previously reported that quinic acid has an effect, especially on foodborne pathogens, and inhibits *S. aureus* by reducing the membrane fluidity, damaging and inhibiting the cell membrane, and also has an antimicrobial effect on *E.coli, Salmonella enterica, Bacillus cereus, Clostridium perfringens* bacteria [32]. Quinic acid damages L-lysine and peptidoglycan synthesis to inhibit cell wall synthesis [33]. In addition, it has been reported that quinic acid prevents bacterial biofilm formation against *P. aeruginosa* and can be used against *P. aeruginosa*-related infections [34]. This study found results supporting this conclusion. In addition, it was determined that quinic acid inhibited *K. pneumoniae, S. pyogenes* bacteria, but did not have an antifungal effect. Because of these properties, quinic acid can be used as a preservative in foods, as well as in the treatment of various infections.

4. Conclusion and Suggestions

In the antioxidant experiments performed with 7 different methods, it was observed that the antioxidant property of quinic acid was not found in DPPH, ABTS, CUPRAC, FRAP, Fe^{3+} reduction methods, but it was very low in DMPD and total antioxidant methods. In addition, antimicrobial activity studies have shown that quinic acid can be used as a good antimicrobial agent. It has been shown that quinic acid can be used efficiently in biotechnological products with antimicrobial properties.

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Contributions of the authors

Author 1: Writing-original draft preparation, data collection, data curation, visualization, analysis, data interpretation. Author 2: Conceptualization, methodology, validation, writing review, editing, supervision, provision of analysis tools. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Conflict of Interest Statement

There is no conflict of interest between the authors.

Statement of Research and Publication Ethics

The study is complied with research and publication ethics.

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