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Investigation of *in vitro* antimicrobial activities of some hydroxybenzoic and hydroxycinnamic acids commonly found in medicinal and aromatic plants

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ABSTRACT

Since hospital-acquired microorganisms are developing more and more resistance to antibiotics used today, researchers are turning to new searches in the treatment of infectious diseases. Unfortunately, unconscious use of antibiotics is another important reason why microorganisms develop resistance to infectious diseases. The aim of this study was to test the antimicrobial activity of some hydroxybenzoic and hydroxycinnamic acids on various gram-positive and gram-negative bacteria and a yeast strain (*C. albicans*). Agar well diffusion and minimum inhibitory concentration (MIC) tests were applied to determine the antimicrobial activities of phenolic acids. Considering the activity findings of phytochemicals on all test microorganisms, they were ranked in terms of their activities with a statistical method called the relative inhibitory capacity index (RICI) (a method that was first introduced in the literature by the current study). RICI analysis showed that the most effective phenolic acids for all test microorganisms were sinapic acid and 4-hydroxybenzoic acid. The RICI coefficients of these compounds were 1.02 and 0.99, respectively. Sinapic acid exhibited a zone of inhibition of 9.00-27.00 mm and an MIC of 18.00-72.00 mg/ml on microorganisms. Inhibition zone and MIC value ranges of 4-hydroxybenzoic acid were determined as 9.00-16.00 mm and 36.00-72.00 mg/ml, respectively. RICI analyzes confirmed that 2-phenylbutyric acid and phloroglucinol carboxylic acid did not show any antimicrobial activity. It is thought that sinapic acid and 4-hydroxybenzoic acid can be used as alternative antimicrobial agents against multi drug resistant microorganisms.

1. Introduction

Hospital-acquired infections are often extremely resistant to antibiotics (Liu et al., 2020). Antibiotic-resistant microorganisms cause the death of hundreds of thousands of people worldwide every year. If a strategy to effectively combat microorganisms resistant to antibiotics is not implemented, it is estimated that the microorganisms showing resistance to the current antibiotics will cause the death of more than half of the patients who die of cancer by 2050 (Ventola, 2015). In order to combat this problem, researchers are trying to discover new and more effective compounds by focusing on the antimicrobial activities of phytochemicals.

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Plants have been used effectively in the treatment of various diseases for centuries. It has been shown that some plant species and foodstuffs containing plant-based compounds (for example, honey) accelerate wound healing and reduce infections in wounds due to the antimicrobial phytochemicals they contain (Efem, 1988; Molan and Betts, 2004). Researchers think that phenolic acids are mainly responsible for the antimicrobial activities of plants or plant-derived foods (Wahdan, 1998). In some studies, it has been proven that phenolic acids successfully eliminate multi-drug resistant microorganisms (Merkl et al., 2010; Nascimento et al., 2000; Wahdan, 1998).

Phenolic acids are low molecular weight compounds that contain a carboxylic acid group in their structure (Monroe et al., 2018). These compounds are secondary metabolites that the plant produces to defend itself against microbial pathogens. Phenolic compounds have lethal effects on microorganisms through different mechanisms. These mechanisms include destabilization of the bacterial membrane, change in plasma permeability, inhibition of enzymes

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produced by microorganisms, disruption of microbial metabolism (for example, protein synthesis), and deprivation of the substrates required for the growth of microorganisms (Dietrich and Nikfardjam, 2017). In a study by Borges et al. (2013), it was reported that phenolic acids affect the polarity by changing the surface electron acceptors of bacteria, and accordingly, they show stronger antimicrobial effects in gram-negative bacterial strains than gram-positive ones.

Phenolic acids show promising potential in curing infections caused by antibiotic-resistant microorganisms and accelerating wound healing. Researchers focus on the use of phenolic acids to combat both hospital-acquired infections (e.g. *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Escherichia coli*, etc.) and pathogens responsible for food spoilage. However, the effectiveness of many phenolic acids on microorganisms has not yet been fully elucidated. Some researchers have published conflicting data on the antimicrobial activities of phenolic acids (Chatterjee et al., 2015; Merkl et al., 2010).

The aim of this study is to investigate the in vitro antimicrobial activities of some hydroxybenzoic and hydroxycinnamic acids commonly found in medicinal and aromatic plants. In antimicrobial activity studies carried out to date, the activity potentials of total extracts, also called crude extract, have been evaluated rather than individual phytochemicals. There are a limited number of studies evaluating the antimicrobial activities of phytochemicals individually. On the other hand, speculative discourses on this subject still continue. It is thought that elucidating the antimicrobial activities of at least some phenolic acids with this study may be beneficial in terms of ending the speculations on this subject. The antimicrobial activities of these components were evaluated both qualitatively and quantitatively. In the qualitative part of the study, first of all, the activity potentials of standard phytochemicals were determined by the agar well diffusion method and the obtained findings were quantitatively confirmed by the minimum inhibitory concentration (MIC) assay.

2. Materials and methods

2.1. Hydroxybenzoic and hydroxycinnamic acids used in the study

In this study, the antimicrobial activities of the following phytochemicals were investigated: gallic acid (1), protocatechuic acid ethyl ester (2), vanillic acid (3), 4-hydroxybenzoic acid (4), ferulic acid (5), caffeic acid (6), *p*-coumaric acid (7), sinapic acid (8), *trans*-cinnamic acid (9), *(-)*-quinic acid (10), rosmarinic acid (11), *o*-coumaric acid (12), valeric acid (13), 2-phenylbutyric acid (14), *(±)*-jasmonic acid (15), methyl paraben (16), propyl paraben (17), phloroglucinol carboxylic acid (2,4,6-trihydroxybenzoic acid) (18) and gallic acid trimethyl ether (3,4,5-trimethoxybenzoic acid) (19) (Figure 1). All the compounds were purchased from Sigma-Aldrich (St. Louis, Missouri, ABD).

2.2. Test microorganisms

In this study *Escherichia coli* ATCC 35218, *Klebsiella pneumoniae* NCTC 5046, *Candida albicans* ATCC 10231, *Salmonella typhi* NCTC 9394, *Pseudomonas aeuroginosa* ATCC 27853, *Shigella boydii* NCTC 9359, *Shigella dysanteriae* NCTC 9762, *Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* ATCC 25923, *Proteus vulgaris* RSHM 96022, and *Corynebacterium diphteriae* RSHM 633 strains were used. Bacteria were incubated overnight in Mueller Hinton Agar (MHA) at 37 °C. *C. albicans* was incubated at 30 °C in Sabouraud Dextrose Agar (SDA) medium.

Two different methods were used in activity tests. Each test was repeated three times.

2.3. Agar well diffusion method

Antimicrobial activities of hydroxybenzoic and hydroxycinnamic acids were determined by the agar well diffusion method. According to this method, standard bacterial strains were cultured at 37 °C overnight in Mueller Hinton Agar medium and *C. albicans* was cultured at 30 °C overnight in Sabouraud Dextrose Agar medium, and then suspensions conforming to the Mc Farland 0.5 chart were prepared in isotonic sodium chloride (NaCl) solution (108 cfu/µl for bacteria, 106 cfu/µl for *C. albicans*). Then, wells with a diameter of 6.0 mm were opened with a sterile glass tube and spread cultivation was carried out from each bacterial strain suspension with a swab stick into the agar medium. 25.0 µl of 10 mg/ml solutions of phytochemicals were transferred to the wells. Inhibition zone diameters observed in petri plates after 24 hours of incubation at 37 °C were recorded in mm (Sokmen et al., 1999). At the end of the incubation, the diameters of the inhibition zones formed around the wells loaded with the extract were measured from the bottom surface of the petri plates with the help of a ruler. Standard antibiotic discs Gentamicin and Nystatin were used as positive control agents.

2.4. Determination of the minimum inhibitory concentration (MIC)

The liquid microdilution method recommended by the NCCLS (National Committee for Clinical Laboratory Standards) was used to determine the MIC values of phytochemicals (Sokmen et al., 1999). Mueller Hinton Broth (MHB) for bacteria and Sabouraud Dextrose Broth (SDB) for *C. albicans* were used. Bacterial strains were incubated overnight in MHA at 37 °C. After incubation, 50 µl of medium and 50 µl of microorganisms were placed in each well. In the dilution process of phytochemicals, serial dilutions were carried out starting from 72.00 mg/ml and making the final concentration 4.50 mg/ml. It was then made up with dH_2O so that the total volume was 172.00 µl. In addition, growth control (MHB + microorganism) and sterility control (MHB + phytochemical) tests were applied. Microtiter plates on which the tests were made were incubated for 24 hours at 37 °C for bacteria and 48 hours at 30 °C for *C. albicans* under normal atmospheric conditions. In order to determine the susceptibility of test microorganisms, MIC values of Gentamycin for bacteria and Nystatin for *C. albicans* were also determined in parallel with the experiments. Bacterial growth was detected by re-culturing each well, as well as observing a white precipitate at the bottom of the wells in microtiter plates.

2.5. Determination of relative inhibition capacity index (RICI)

In this study, RICI was applied to statistically rank the activity potentials of phytochemicals using the zone diameter values obtained from the antimicrobial activity analysis. The aforementioned analysis was brought to the literature for the first time by this study by modifying the relative binding capacity index (RBCI) and relative antioxidant capacity index (RACI) methods performed by Istifli et al. (2020) and Sarikurkcu and Zengin (2020), respectively. Using RICI, it is possible to compare statistically relevant data with different scientific meanings. Since the inhibition zones of phytochemicals are different for each microorganism, phytochemicals can only be ranked in terms of their potential at this parameter if they are performed in the light of their inhibition zones only to one microorganism. However, sequencing based on only one of these microorganisms cannot represent the full activity potential of these molecules. The most common method used to calculate the

interaction between each phytochemical and microorganism is the "central bias" in which components are ranked according to the mean value of each component.

If the values (inhibition zone) in each data set are converted into standard scores, it is possible to compare them with each other. Arithmetic mean and standard deviation values were calculated for each phytochemical by using the inhibition zones of the molecules. Raw standard scores were obtained by subtracting the inhibition zones of each phytochemical for each microorganism from this arithmetic mean and then dividing by the standard deviation value (see equation given below) (Sharma, 1996). The RICI values of each phytochemical were then calculated by taking the average of these standard scores obtained separately for each microorganism target.

$$Standard\ score = (x- \mu)/ \sigma$$

where 'x' is the raw data, 'μ' is the mean, and 'σ' is the standard deviation.

3. Results and discussion

In order to determine the antimicrobial activities of hydroxybenzoic and hydroxycinnamic acids, agar well diffusion method, which is a qualitative test system, was first applied (Tables 1, 2 and 3). Then, the MIC test was performed to determine the concentration range in which phytochemicals inhibit the growth of microorganisms (Tables 4 and 5).

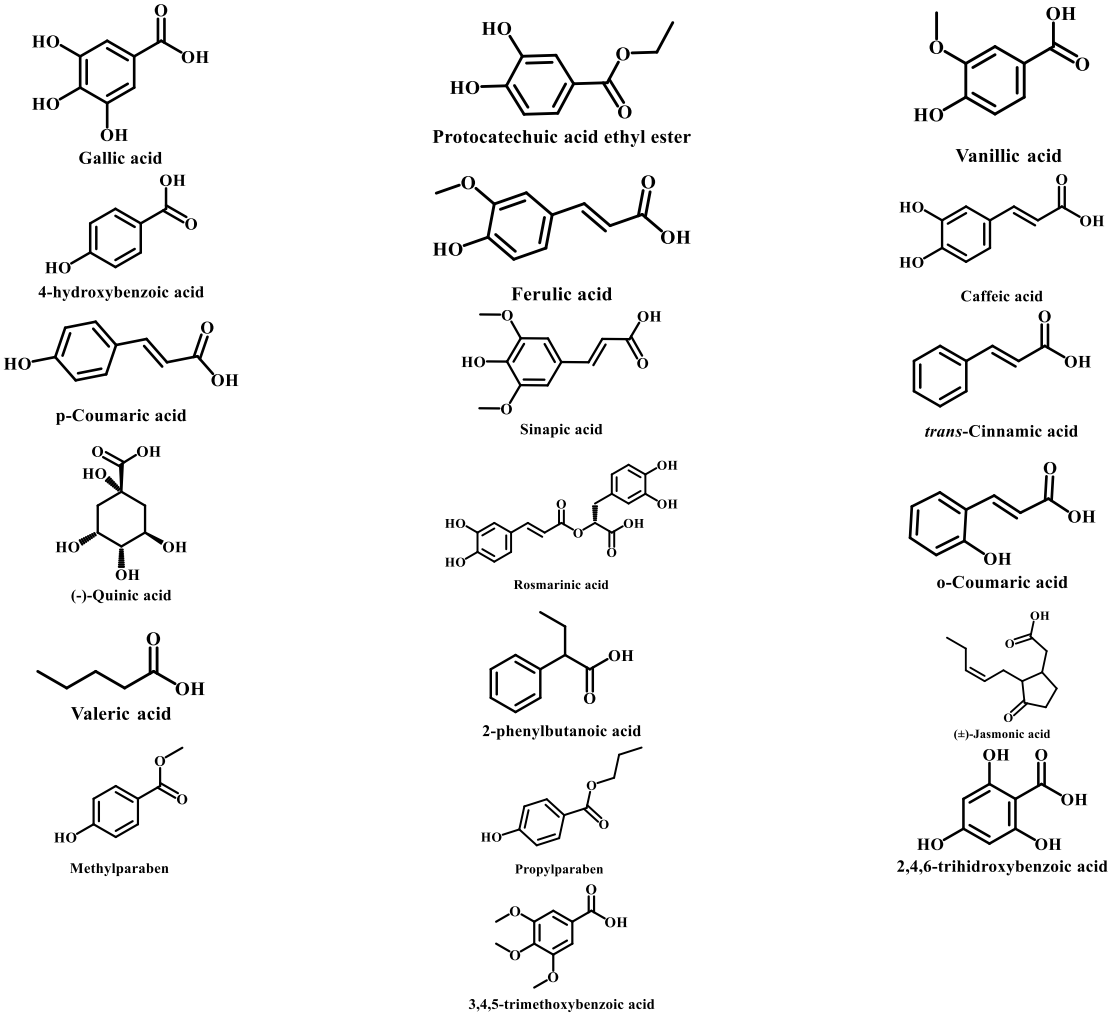

Figure 1. Chemical structures of compounds

Considering the data obtained as a result of the agar well diffusion method, it was determined that all phytochemicals except 2-phenylbutyric acid and phloroglucinol carboxylic acid exhibited various levels of antimicrobial activity on test microorganisms. Gallic acid, vanillic acid, 4-hydroxybenzoic acid, sinapic acid, *trans*-cinnamic acid, rosmarinic acid, *o*-coumaric acid and *(±)*-jasmonic acid were effective on all microorganisms, while protocatechuic acid ethyl ester, ferulic acid, caffeic acid, *p*-coumaric acid, *(-)*-quinic acid, valeric acid, methyl paraben, propyl paraben and gallic acid trimethyl ether did not show any effect on some microorganisms.

When the resistance and/or sensitivity of test microorganisms against phytochemicals were evaluated, the most sensitive ones were determined as *S. boydii*, *S. dysanteriae* and *S. aureus*. Most of the phytochemicals showed stronger activity on the microorganisms in question than gentamycin, which was used as a positive control agent.

The data obtained from the RICI analysis, in which the activities of phenolic acids against all test microorganisms were evaluated as a whole, are given in Figure 2. The data in the figure in question showed that the most effective phenolic acids for all test microorganisms were sinapic acid and 4-hydroxybenzoic acid. The RICI coefficients of these compounds were 1.02 and 0.99, respectively. Sinapic acid exhibited an inhibition zone of 9.00-27.00 mm and a MIC value of 18.00-72.00 mg/ml on the microorganisms. Inhibition

zone and MIC value ranges of 4-hydroxybenzoic acid were determined as 9.00-16.00 mm and 36.00-72.00 mg/ml, respectively. RICI analyzes confirmed that 2-phenylbutyric acid and phloroglucinol carboxylic acid failed to show any antimicrobial activity. The RICI coefficient of both phenolic acids was determined as -1.48.

Table 1. Antimicrobial activities of compounds 1-6 obtained as a result of the agar well diffusion assay [1]

Microorganisms	Compounds						Controls	
	1	2	3	4	5	6	Gentamycin[2]	Nystatin[2]
S. typhi	9.00 ± 0.12^{bc}	8.00 ± 0.20^{ab}	11.00 ± 0.73^{de}	12.00 ± 0.14^{e}	-	-	10.00 ± 0.45^{cd}	n.t. [3]
P. aeruginosa	6.00 ± 0.63^{a}	-	8.00 ± 0.23^{abc}	9.00 ± 0.06^{bc}	-	-	20.00 ± 1.06^{d}	n.t.
S. boydii	13.00 ± 0.42^{bcd}	12.00 ± 0.79^{bc}	15.00 ± 1.40^{def}	16.00 ± 0.76^{efg}	16.00 ± 0.22^{efg}	13.00 ± 0.46^{bcd}	12.60 ± 0.20^{abcd}	n.t.
S. dysanteriae	7.00 ± 0.26^{ab}	6.00 ± 0.06^{a}	9.00 ± 0.22^{ab}	10.00 ± 0.40^{bc}	25.00 ± 1.14^{ijk}	23.00 ± 2.08^{ghi}	13.50 ± 0. 00^{cd}	n.t.
B. subtilis	13.00 ± 1.10^{ef}	12.00 ± 1.20^{de}	15.00 ± 1.16^{fg}	16.00 ± 0.48^{g}	6.00 ± 0.26^{a}	12.00 ± 0.22^{de}	29.00 ± 1.15^{h}	n.t.
K. pneumoniae	7.00 ± 0.20^{ab}	6.00 ± 0.26^{a}	9.00 ± 0.08^{cd}	10.00 ± 0.06^{d}	-	-	20.00 ± 0.70^{e}	n.t.
S. aureus	18.00 ± 1.40^{cde}	17.00 ± 1.14^{cd}	20.00 ± 1.54^{def}	21.00 ± 0.80^{efg}	25.00 ± 1.22^{hij}	11.00 ± 0.06^{a}	23.00 ± 0.76^{fgh}	n.t.
E. coli	8.00 ± 0.74^{ab}	7.00 ± 0.32^{a}	10.00 ± 0.82^{cd}	11.00 ± 0.42^{d}	-	-	16.00 ± 0.96^{e}	n.t.
P. vulgaris	7.00 ± 0.22^{ab}	6.00 ± 0.18^{a}	9.00 ± 0.14^{bc}	10.00 ± 0.14^{c}	6.00 ± 0.06^{a}	-	22.00 ± 1.40^{d}	n.t.
C. diphteriae	7.00 ± 0.14^{ab}	6.00 ± 0.14^{a}	9.00 ± 0.26^{cd}	10.00 ± 0.22^{d}	7.00 ± 0.40^{ab}	10.00 ± 0.43^{d}	23.00 ± 0.10^{f}	n.t.
C. albicans	12.00 ± 0.74^{d}	11.00 ± 0.84^{cd}	14.00 ± 0.40^{e}	15.00 ± 0.26^{e}	10.00 ± 0.08^{bc}	11.00 ± 0.07^{cd}	n.t.	n.t.

[1] The measured inhibition zone diameter includes the well diameter of 6.0 mm. Values indicated by the same superscripts within the same row are not different from the honestly significant difference after Tukey's post hoc test at 5% significance level.
[2] The concentration of antibiotics is 30 μg/disc.
[3] n.t.: Not tested

In studies carried out by some researchers on both gram-negative and gram-positive bacterial species, it has been reported that sinapic acid has an inhibitory activity of 97-99% on microorganisms (Nowak et al., 1992). In another study conducted by Engels et al. (2012), it was determined that this compound had a lethal effect only on sinapic acid-resistant microorganisms without harming the lactic acid bacteria in the environment. There are also reports that sinapic acid or some of its derivatives exhibit antifungal activity (Kelly et al., 2008).

Table 2. Antimicrobial activities of compounds 7-12 obtained as a result of the agar well diffusion assay [1]

Microorganisms	Compounds						Controls	
	7	8	9	10	11	12	Gentamycin[2]	Nystatin[2]
S. typhi	-	10.00 ± 0.24^{cd}	7.00 ± 0.12^{a}	-	8.00 ± 0.76^{ab}	7.00 ± 0.10^{a}	10.00 ± 0.45^{cd}	n.t. [3]
P. aeruginosa	-	10.00 ± 0.63^{c}	7.00 ± 0.24^{ab}	-	8.00 ± 0.96^{abc}	7.00 ± 0.04^{ab}	20.00 ± 1.06^{d}	n.t.
S. boydii	15.00 ± 1.08^{def}	17.00 ± 0.82^{fgh}	18.00 ± 0.16^{gh}	14.00 ± 0.44^{cde}	19.00 ± 0.40^{h}	16.00 ± 0.69^{efg}	12.60 ± 0.20^{abcd}	n.t.
S. dysanteriae	24.00 ± 0.73^{hij}	27.00 ± 1.60^{lk}	27.00 ± 0.49^{jk}	18.00 ± 0.32^{ef}	28.00 ± 2.15^{k}	26.00 ± 0.67^{ijk}	13.50 ± 0. 00^{cd}	n.t.
B. subtilis	-	16.00 ± 0.89^{g}	8.00 ± 0.06^{ab}	13.00 ± 0.15^{ef}	9.00 ± 0.16^{bc}	15.00 ± 0.07^{fg}	29.00 ± 1.15^{h}	n.t.
K. pneumoniae	-	9.00 ± 0.06^{cd}	7.00 ± 0.14^{ab}	-	7.00 ± 0.10^{ab}	8.00 ± 0.50^{bc}	20.00 ± 0.70^{e}	n.t.
S. aureus	24.00 ± 1.42^{ghi}	17.00 ± 0.14^{cd}	27.00 ± 1.26^{ij}	13.00 ± 0.45^{ab}	28.00 ± 1.06^{j}	16.00 ± 0.15^{bc}	23.00 ± 0.76^{fgh}	n.t.
E. coli	-	9.00 ± 0.49^{bc}	7.00 ± 0.04^{a}	-	7.00 ± 0.12^{a}	7.00 ± 0.06^{a}	16.00 ± 0.96^{e}	n.t.
P. vulgaris	-	9.00 ± 0.12^{bc}	8.00 ± 0.26^{abc}	-	8.00 ± 0.90^{abc}	7.00 ± 0.12^{ab}	22.00 ± 1.40^{d}	n.t.
C. diphteriae	6.00 ± 0.76^{a}	15.00 ± 0.24^{e}	9.00 ± 0.84^{cd}	10.00 ± 0.20^{d}	9.00 ± 0.76^{cd}	14.00 ± 0.60^{e}	23.00 ± 0.10^{f}	n.t.
C. albicans	-	10.00 ± 0.16^{bc}	7.00 ± 0.46^{a}	9.00 ± 0.10^{b}	11.00 ± 0.06^{cd}	9.00 ± 0.54^{b}	n.t.	25.00 ± 0.90

[1] The measured inhibition zone diameter includes the well diameter of 6.0 mm. Values indicated by the same superscripts within the same row are not different from the honestly significant difference after Tukey's post hoc test at 5% significance level.
[2] The concentration of antibiotics is 30 μg/disc.
[3] n.t.: Not tested

Table 4. Antimicrobial activities of compounds 1-10 obtained as a result of MIC assay (mg/ml)

Microorganisms	Compounds									
	1	2	3	4	5	6	7	8	9	10
S. typhi	72.00	72.00	72.00	72.00	> 72.00	> 72.00	> 72.00	72.00	72.00	> 72.00
P. aeruginosa	72.00	> 72.00	72.00	72.00	> 72.00	> 72.00	> 72.00	72.00	72.00	> 72.00
S. boydii	72.00	72.00	36.00	36.00	72.00	72.00	36.00	36.00	36.00	72.00
S. dysanteriae	72.00	72.00	72.00	72.00	36.00	36.00	36.00	18.00	18.00	36.00
B. subtilis	72.00	72.00	72.00	36.00	72.00	72.00	> 72.00	36.00	72.00	72.00
K. pneumoniae	72.00	72.00	72.00	72.00	> 72.00	> 72.00	> 72.00	72.00	72.00	> 72.00
S. aureus	36.00	36.00	36.00	36.00	36.00	72.00	36.00	36.00	18.00	72.00
E. coli	72.00	72.00	72.00	72.00	> 72.00	> 72.00	> 72.00	72.00	72.00	> 72.00
P. vulgaris	72.00	72.00	72.00	72.00	72.00	> 72.00	> 72.00	72.00	72.00	> 72.00
C. diphteriae	72.00	72.00	72.00	72.00	72.00	72.00	72.00	36.00	72.00	72.00
C. albicans	72.00	72.00	36.00	36.00	72.00	72.00	> 72.00	72.00	72.00	72.00

[1] The concentration of antibiotics is 30 g/disc.
[2] n.t.: Not tested

There are also some reports in the literature that 4-hydroxybenzoic acid has antimicrobial activity. In a study by Cho et al. (1998), this compound was reported to be effective on many gram-negative and gram-positive microorganisms tested.
In addition to the literature data given above, there are some data in the literature regarding the antimicrobial activities of some of the hydroxycinnamic and hydroxybenzoic acids analyzed in the present study. In a study carried out by Merkl et al. (2010), antimicrobial activities of some phenolic acids and their derivatives were reported. The data obtained from the aforementioned study support those in the current study.

Table 5. Antimicrobial activities of compounds 11-19 obtained as a result of MIC assay (mg/ml)

Microorganisms	Compounds								
	11	12	13	14	15	16	17	18	19
S. typhi	72.00	72.00	72.00	> 72.00	72.00	72.00	> 72.00	> 72.00	> 72.00
P. aeruginosa	72.00	> 72.00	72.00	> 72.00	72.00	> 72.00	> 72.00	> 72.00	> 72.00
S. boydii	36.00	36.00	36.00	> 72.00	36.00	72.00	72.00	> 72.00	72.00
S. dysanteriae	18.00	18.00	36.00	> 72.00	36.00	> 72.00	72.00	> 72.00	36.00
B. subtilis	72.00	72.00	72.00	> 72.00	72.00	72.00	72.00	> 72.00	72.00
K. pneumoniae	72.00	72.00	72.00	> 72.00	72.00	> 72.00	> 72.00	> 72.00	> 72.00
S. aureus	18.00	36.00	36.00	> 72.00	18.00	72.00	36.00	> 72.00	36.00
E. coli	72.00	72.00	72.00	> 72.00	72.00	72.00	> 72.00	> 72.00	> 72.00
P. vulgaris	72.00	72.00	72.00	> 72.00	> 72.00	> 72.00	> 72.00	> 72.00	> 72.00
C. diphteriae	72.00	72.00	> 72.00	> 72.00	> 72.00	> 72.00	> 72.00	> 72.00	> 72.00
C. albicans	72.00	72.00	72.00	> 72.00	72.00	72.00	> 72.00	> 72.00	> 72.00

[1] The concentration of antibiotics is 30 g/disc.
[2] n.t.: Not tested

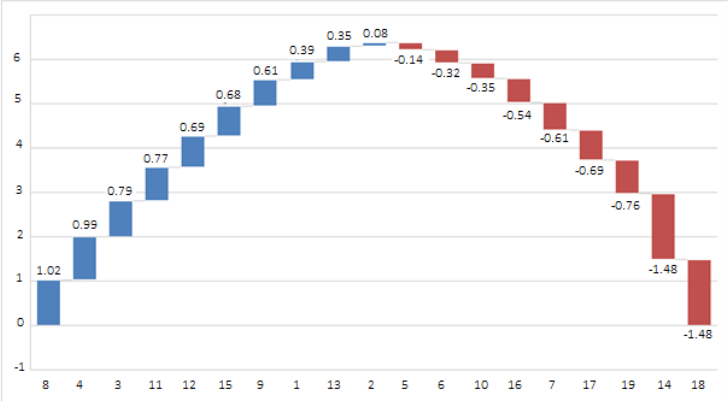

Figure 2. Sorting phytochemicals from strongest to weakest according to the RICI values

4. Conclusions

In this study, antimicrobial activities of some hydroxybenzoic and hydroxycinnamic acids on gram-negative and gram-positive bacteria and *C. albicans* were analyzed. According to the results obtained, it has been concluded that sinapic acid and 4-hydroxybenzoic acid can be used as alternative antimicrobial agents today, where hospital-acquired infectious agents make treatment with existing antimicrobial drugs difficult.

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Conflict of interest

The author confirms that there are no known conflicts of interest.

CRediT authorship contribution statement

Aslihan Gurbuzer: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing, Review & Editing

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