Original Article Ann Med Res 2024;31(3):222–227

Ann Med Res

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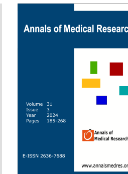

The inhibitory effects of taxifolin, namely dihydroquercetin as a pharmaceutical agent on the growth of bacterial and fungal species

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ARTICLE INFO

Keywords:
Taxifolin
Dihydroquercetin
Antibacterial activity
Antifungal activity
Pharmaceutical agent
Antimicrobials

Received: Jan 22, 2024
Accepted: Mar 04, 2024
Available Online: 25.03.2024

DOI:
10.5455/annalsmedres.2024.01.017

Abstract

Aim: Taxifolin (dihydroquercetin) is a natural bioactive flavonoid with antifungal, antiviral, antibacterial, antioxidant, and anti-inflammatory properties, and is a valuable compound in the medical, pharmaceutical, and food industries. This study aims to determine the Minimum Inhibitory Concentration (MIC) of pure taxifolin (99.25%) against pathogenic and opportunistic microorganisms.

Materials and Methods: The antibacterial and antifungal activities of taxifolin against two Gram-positive (*E. aerogenes, S. aureus*), three Gram-negative (*P. aeruginosa, K. pneumonia* and *E. coli*), and four yeast strains (*C. krusei, C. glabrata, C. tropicalis* and *C. albicans*) was determined using agar and broth microdilution methods.

Results: The MIC value for tested Gram-positive bacteria is 1 mg/mL, which is 2 mg/ml for Gram-negative bacteria. At the same time, the MIC value was 8 mg/mL for all *Candida* species tested except *C. glabrata* (MIC: 4 mg/mL).

Conclusion: In conclusion, it was determined that the antibacterial property of taxifolin was more pronounced than its antifungal properties. Taxifolin is a natural compound with high medical and pharmacological value. This study proved the effectiveness of pure taxifolin as a pharmacotherapeutic agent on pathogenic and opportunistic microorganisms. The preliminary data collected in this study should be further supported, and *in vivo* and bioavailability studies should be detailed in future studies.

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Introduction

In recent years, antimicrobial resistance developed by microorganisms has been a significant global public health problem. According to estimates from the World Health Organization, more than 670,000 diseases are caused by antibiotic-resistant bacteria annually in European countries, resulting in more than 33,000 human deaths [1]. Antimicrobial resistance occurs due to the uncontrolled use of antibiotics and threatens public health worldwide, including in African countries [2, 3]. Along with antimicrobial resistance, increased drug consumption and the number of patients treated create a severe economic burden [4, 5, 6, 7]. Suppose the resistance rate continues to increase at the current rate. In that case, it is estimated that 10 million people will die every year by 2050, and a loss of 100 trillion dollars will occur in the global economy. For our country, Turkey, it is estimated that resistance will have a burden of 220 billion dollars, according to the optimistic scenario, and 1.4 trillion dollars, according to the pessimistic scenario, by 2050 [8]. It has been observed that bacteria belonging to the *P. aeruginosa, S. aureus, Enterobacteriaceae* and *Enterococcus* genus have developed significant antibiotic resistance [9]. Excessive and misuse of antibiotics pose both a significant threat to public health and a financial burden. Therefore, research on new, natural antibiotics that do not create an economic burden has become the focus of attention. The usability of substances obtained from natural sources, such as plant-derived phenolic compounds, in primary care is promising.

Taxifolin (dihydroquercetin) is a natural flavanonol, a type of flavonoid that is found in many plant ingredients [10, 11, 12]. Studies have proven the medical and pharmaceutical value of taxifolin, and the anticancer antioxidant, antimicrobial, and anti-inflammatory effects of pure taxifolin or as a component of a plant were investigated [13, 14, 15]. Taxifolin can prevent the growth and metastasis of tumor cells by inhibiting fatty acid synthesis in cancer cells [16]. It has been investigated that taxifolin can be used for treatment in cases of major inflammatory diseases

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[10, 12]. Taxifolin inhibits cancer cell migration, proliferation, and invasion via some signaling pathways and may be an effective therapeutic agent for treating osteosarcoma [12]. It has been found that taxifolin and other flavonoids with similar molecular structures can act as "enhancers" in combination with Andrographolide, which suppresses the proliferation of cancer cells and triggers apoptosis in the treatment of prostate cancer and can inhibit breast cancer cells with a dose-dependent effect [16, 17]. Furthermore, taxifolin has potent antioxidant and antiradical activities due to its structure consisting of two aromatic rings containing two phenolic groups (-OH) in the meta and para positions [18]. It reduces lipid oxidation in food or pharmaceutical products and delays the formation of toxic oxidation products [19]. In an experimental animal study, taxifolin had antioxidant activity and a capillary protective effect [20]. Although many studies have been conducted on the effectiveness of taxifolin against cancer cells and its antioxidant properties, studies on the antimicrobial properties of taxifolin are limited.

Taxifolin has been used for treatment purposes in patients with methicillin-resistant S. aureus (MRSA) infection. Taxifolin has been determined to increase the effectiveness of some antibiotics, such as ceftazidime and levofloxacin [21]. So far, studies on the antimicrobial properties of taxifolin have mainly been carried out using taxifolin obtained from plant sources, or the proven antimicrobial properties of plants have been attributed to the taxifolin contained in them [10, 22, 23]. In this study, unlike the studies done so far in the literature, pure taxifolin's antibacterial and antifungal properties were investigated. Consequently, the effective Minimum Inhibitory Concentration (MIC) values of taxifolin against the tested microorganism types were determined.

Materials and Methods

Taxifolin

100 mg of taxifolin ($C_{15}H_{12}O_7$) was purchased from AmBeed (CAS: 480-18-2, Illinois, USA). The structural formulation of taxifolin is demonstrated in Figure 1. The molecular weight of taxifolin is 304.25 with a purity of 99.25%, and its synonym is dihydroquercetin or (2R,3R)-2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxychroman-4-one. It was dissolved in dimethyl sulfoxide (DMSO) (CAS: 67-68-5, Sigma, Steinheim, Germany).

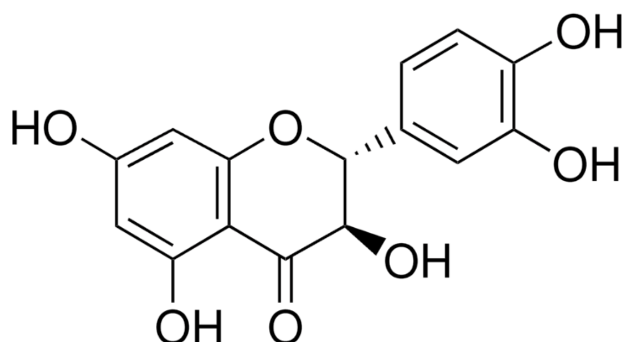

Figure 1. Chemical structure of taxifolin ($C_{15}H_{12}O_7$).

Strains and culture media

Nine different microorganisms, including two Gram-positive, three Gram-negative, and four yeast species, were used in the antimicrobial activity determination tests. Except for *E. coli* (C2987, New England Biolabs, MA, USA), all microorganisms, including *Enterobacter aerogenes* (ATCC 51697), *Staphylococcus aureus* (ATCC 12600), *Pseudomonas aeruginosa* (ATCC 10145) *Klebsiella pneumoniae* (ATCC 13883), *Candida krusei* (ATCC 14243), *Candida glabrata* (ATCC 2001), *Candida tropicalis* (ATCC 13803), and *Candida albicans* (ATCC 14053) were obtained from the American Type Culture Collection (VA, USA). While Muller hinton agar (Merk, Darmstadt, Germany) and Muller hinton broth (Himedia, Nashik, India) were used for bacterial species; sabouraud broth (Biolife, Milan, Italy) and sabouraud 4 % glucose agar (Chemsolute, Renningen, Germany), which provide optimum conditions, were used for yeast species.

Determination of antimicrobial activity using broth microdilution method

The broth and agar dilution methods were performed as before with minor changes [24]. 28.8 mg of taxifolin powder was dissolved in 180 µL of DMSO. 20 µl of the prepared taxifolin DMSO solution was distributed to the first wells containing 180 µL of broth media, and two-fold dilutions were made starting from the first well to the tenth well. After dilutions, the first well contained 8 mg/mL taxifolin, and the last (10th) well included 0.0156 mg/mL taxifolin with a total volume of 200 µL. The entire protocol was applied in the same way for both fungal and bacterial species, but for fungal species, dilution was started from a higher concentration. Therefore, the first well contains 16 mg/mL taxifolin, and the tenth well contains 0.312 mg/mL taxifolin. All bacterial and fungal species were suspended in distilled water, and turbidity was set to 0.5 McFarland (equal to $1\text{-}1.5\times10^8$ CFU/mL for bacterial strains, $1\text{-}1.5\times10^6$ CFU/mL for fungal species). After that, 1 µL of each microbial strain was inoculated to the wells that contained different concentrations of taxifolin. 11th and 12th wells were arranged as positive and negative controls, respectively. Subsequently, the microplates were incubated at 35 ^oC for 24 hours. The next day, 15 µL of 0.15% (w/v) resazurin sodium salt (Sigma, Darmstadt, Germany) was added to each well, and microplates were left to stand in the incubator at 35 °C for 3-4 hours. Then, the color change was observed, confirming bacterial cell growth.

Determination of antimicrobial activity using agar dilution method

For the agar dilution assay, 96 mg of taxifolin was dissolved in 2.16 mL DMSO, and this solution was added to 9.84 mL muller hinton broth media. The final broth solution was diluted twofold to obtain a taxifolin concentration of 8 mg/mL in the first agar plate. Twice all these rates were prepared for yeast species. Thus, for yeast species, the amount of taxifolin in the first sabouraud glucose agar plate was 16 mg/ml after two-fold dilution. Prepared

Muller Hinton agar plates containing taxifolin at different concentrations were divided into five zones for bacterial species. Sabouraud glucose agar plates containing different concentrations of taxifolin were divided into four zones for yeast species. All bacterial and fungal species were inoculated in distilled water, and turbidity was set to 0.5 McFarland. Then, 1 µL of different bacterial strains was inoculated into each zone of the muller hinton agar plates, and 1 µL of the yeast strains into each zone of the sabouraud glucose agar plates. From the first to the fifth zone of the muller hinton agar plates, *E. aerogenes*, *S. aureus*, *P. aeruginosa*, *K. pneumonia*, and *E. coli* strains were inoculated, respectively. Moreover, from the first to the fourth zone of the sabouraud glucose agar plates, *C. krusei*, *C. glabrata*, *C. tropicalis*, and *C. albicans* strains were inoculated, respectively. The plates were incubated at 35 ^{o}C for 24 hours. The next day, the growth of bacteria on the plate was observed.

Results

Results of antibacterial activity assays

After overnight incubation, all plates and microplates were evaluated to determine MIC (Minimum Inhibitory Concentration) values. MIC values were determined as defined by the Clinical and Laboratory Standards Institute [25]. As a result of the agar dilution method, *E. aerogenes* and *S. aureus* colonies began to form starting from the E plate, where the taxifolin concentration was 0.5 mg/mL. Thus, the MIC value of taxifolin against *E. aerogenes* and *S. aureus* was found to be 1 mg/mL. Colonies of *P. aeruginosa*, *K. pneumonia*, and *E. coli* began appearing from the D plate. So, the MIC value of taxifolin against *P. aeruginosa*, *K. pneumonia*, and *E. coli* was determined to be 2 mg/ml (Figure 2). Plate L is the positive control expressing the viability and purity of all tested bacterial strains.

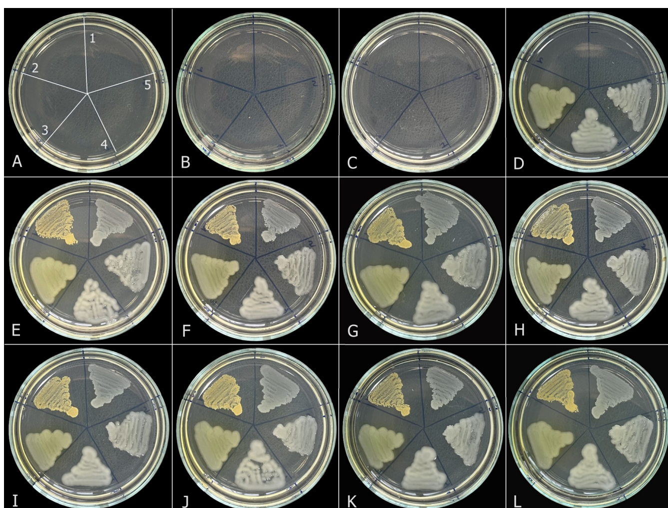

Figure 2. The result of the antibacterial activity assay against *E. aerogenes* (1), *S. aureus* (2), *P. aeruginosa* (3), *K. pneumonia* (4), and *E. coli* (5) using the agar dilution method. Plate concentrations from A to K were 8, 4, 2, 1, 0.5, 0.25, 0.125, 0.063, 0.031, 0.016, and 0.008 mg/mL, respectively. Plate L is the positive control.

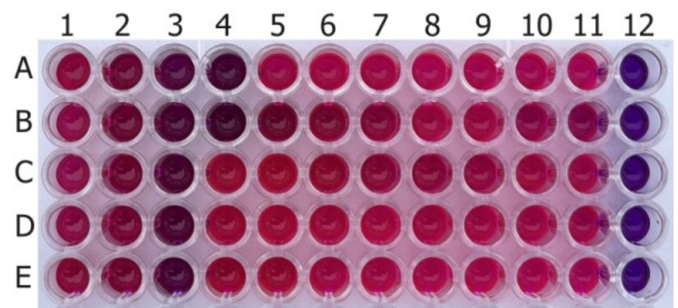

Figure 3. The result of the antibacterial activity assay against *E. aerogenes* (A), *S. aureus* (B), *P. aeruginosa* (C), *K. pneumonia* (D), and *E. coli* (E) using the broth microdilution method. Wells concentrations from 1st to 10th were 8, 4, 2, 1, 0.5, 0.25, 0.125, 0.063, 0.031, and 0.016 mg/mL, respectively. 11th and 12th wells are positive and negative controls, respectively.

The antibacterial activity assay result using the broth microdilution method is demonstrated in Figure 3. According to broth microdilution, it is known that microorganism growth occurs in the wells where the color of the well changes from blue-purple to pink [24, 26]. Consequently, *E. aerogenes* and *S. aureus* grew from the 5th well, while *P. aeruginosa*, *K. pneumonia*, and *E. coli* grew from the 4th well. Therefore, the MIC value for *E. aerogenes* and *S. aureus* is in the 4th well (1 mg/mL), which contains the lowest amount of taxifolin at which no bacterial growth occurs. Additionally, the MIC value of taxifolin against *P. aeruginosa*, *K. pneumonia*, and *E. coli* was 2 mg/mL, the same as the agar dilution method result (Table 1). 11th and 12th wells are positive and negative controls, respectively. The 11th well is the positive control expressing the viability of the microorganism tested in the same row on the microplate. The 12th well is the negative control, confirming no contamination during application. The analyses were performed in triplicate, and the results are expressed as mean.

Table 1. MIC values of taxifolin against different bacterial and fungal species.

Microorganisms	Taxifolin (mg/mL)
E. aerogenes	1
S. aureus	1
P. aeruginosa	2
K. pneumonia	2
E. coli	2
C. krusei	8
C. glabrata	4
C. tropicalis	8
C. albicans	8

Results of antifungal activity assays

In the antifungal activity assay, *C. glabrata* grew from plate D, where the taxifolin concentration was 2 mg/mL.

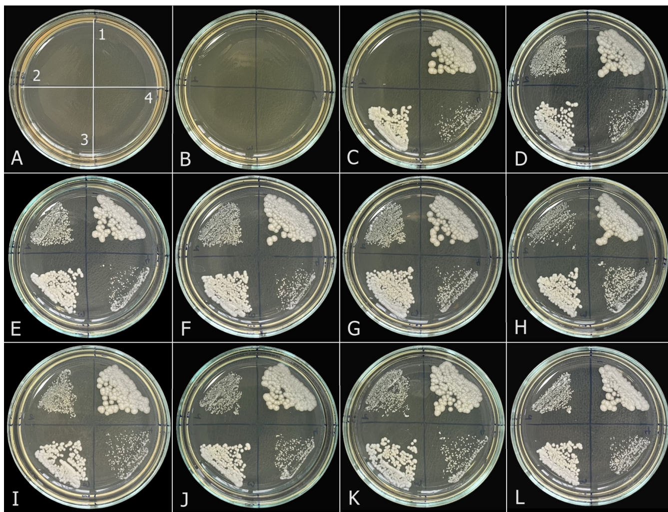

Figure 4. The result of the antifungal activity assay against *C. krusei* (1), *C. glabrata* (2), *C. tropicalis* (3), and *C. albicans* (4) using the agar dilution method. Plate concentrations from A to K were 16, 8, 4, 2, 1, 0.5, 0.25, 0.125, 0.063, 0.031, and 0.016 mg/mL, respectively. Plate L is the positive control.

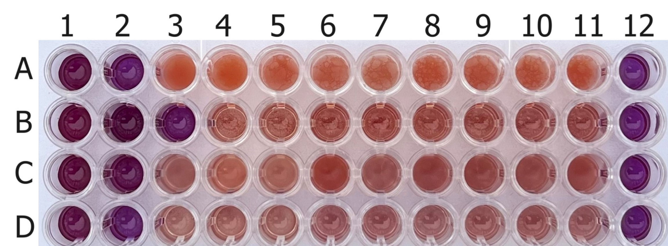

Figure 5. The result of the antifungal activity assay against *C. krusei* (A), *C. glabrata* (B), *C. tropicalis* (C), and *C. albicans* (D) using the broth microdilution method. Wells concentrations from 1st to 10th were 16, 8, 4, 2, 1, 0.5, 0.25, 0.125, 0.063, and 0.031 mg/mL, respectively. 11th and 12th wells are positive and negative controls, respectively.

However, the other *Candida* species tested, including *C. krusei*, *C. tropicalis*, and *C. albicans*, grew from plate C, where the taxifolin concentration was 4 mg/mL. Therefore, while the MIC value of taxifolin against *C. glabrata* was 4 mg/mL, the MIC value against *C. krusei*, *C. tropicalis* and *C. albicans* was determined as 8 mg/mL (Figure 4). Plate L is the positive control expressing the viability and purity of all tested yeast strains.

As a result of the broth dilution method, *C. glabrata* started to grow from 4th well, while other tested *Candida* species started to grow from 3rd well. Therefore, the MIC value of *C. glabrata* is 4 mg/mL, which is the taxifolin concentration in the 3rd well, where no color change was observed. The MIC value of taxifolin against *C. krusei*, *C. tropicalis*, and *C. albicans* was found to be 8 mg/mL, the same as the results of the agar dilution method (Figure 5). The analyses were carried out in triplicate, with zero standard deviation, and all MIC values are shown in Table 1.

Discussion

Plants are rich in secondary plant metabolites such as flavonoids and other pigments. Phenolic acids in plants, such as flavonols, ascorbate, β-carotene, polyphenols, and tocopherols, are natural compounds with many biological activities and are integral to human nutrition [19, 27]. Interest in flavonoids, the most common polyphenolic group, has increased dramatically after their effects on human health were determined by pharmaceutical applications. Phenolic compounds reduce the risk of degenerative diseases, including neurodegenerative diseases, cancer, diabetes, osteoporosis, and cardiovascular diseases [28, 29]. Flavonoids are widely distributed in plants, perform many functions, and constitute a significant class of phenolic compounds and secondary plant metabolites. Flavonoids are generally found in plant cell cavities and leaves as water-soluble glycosides [28]. Flavonoids also protect plant tissues in response to microbial attacks, besides serving as structural agents in plants [30].

Taxifolin is a flavonol subclass of flavonoids and is abundant in citrus fruits, onions, and some plants. Taxifolin is widely used in medicine and pharmaceuticals, and there is much research on its use in public health care [13]. However, so far, studies evaluating the antibacterial and antifungal properties of taxifolin are very limited. A study investigated the inhibitory activity of taxifolin on the pathogenic, opportunistic, and probiotic microorganisms *Staphylococcus epidermidis*, *Micrococcus luteus*, *Escherichia coli*, and *Pseudomonas aeruginosa* [31]. The gel diffusion method evaluated the antimicrobial activity of taxifolin through inhibition zones. As a result, taxifolin showed the most potent inhibition against *S. epidermidis,* with an inhibition zone of 21.33 ± 0.82 mm, but did not exhibit any antimicrobial properties against other microorganisms tested [31]. The antimicrobial activity of *Koompassia malaccensis*, which contains taxifolin and three flavanonols, was evaluated, and the inhibitory effect of wood extract against *Streptococcus sobrinus* was revealed [10]. In a study conducted with taxifolin isolated from Acacia catechu leaves, taxifolin was found to have antibacterial properties against *Streptococcus mutans* and *Lactobacillus acidophilus*, but MIC values were not determined. Further studies and other pharmacological studies were recommended to find the active compound responsible for the antibacterial effects [23]. In *in vitro* and *in silico* analyses by Kozhikkadan Davis et al., the antimicrobial activity of taxifolin against *Mycobacterium tuberculosis* was proven, and its MIC value was determined to be ≤ 12.5 µg/ml. Moreover, taxifolin has been reported to have significant interactions with DNA gyrase and aminoacyl-tRNA synthetases, two critical bacterial enzymes involved in bacterial DNA replication, translation and transcription [32]. In a study conducted with *Pinus sylvestris* and *Picea abies*, the antibacterial activity of phenolic compounds obtained from the extracts of these plants was studied, and the antibacterial activity found was attributed to taxifolin and other flavonoids contained in these plants [22]. In another study, the antifungal activity of five flavonoids

and taxifolin obtained from *Mangifera indica L.* was examined against five different fungal species, predominantly *Aspergillus* species, and significant antifungal activity was observed [33]. Taxifolin inhibits the growth of vancomycin-resistant *S. aureus* (VRSA) in a dose-dependent manner and reduces bacterial viability. Similarly, it attenuates bacterial biofilm production activity in a dose-dependent manner [34]. *In silico* analysis, it was determined that taxifolin is an inhibitor of Tec1 and Rfg1, the main transcriptional factors that induce hyphal growth of *C. albicans* [35]. In another study, the MIC values of taxifolin (>96%), purified from *Rhizoma Smilacis Glabrae*, against *E. coli* and *S. aureus* were found to be 1.11 mg/mL and 0.556 mg/mL, respectively [36]. Taxifolin was found to exhibit antimicrobial activities against *S. aureus* and *P. acnes* in the paper-disc assay. MIC experiments reveal that taxifolin exhibited the highest antimicrobial activity at 625 µg/mL against *P. acnes*, 2,500 µg/mL against *S. aureus*, and 5,000 µg/mL against *E. coli* [37]. Apart from all these *in vitro* and *in silico* studies, taxifolin *in vivo* promotes the elimination of *S. aureus*, *P. aeruginosa*, and *C. albicans* from wounds [38].

Many studies attribute the antimicrobial properties of plants to the phenolic compounds they contain and state that the chemical structure of these compounds affects the antimicrobial properties. For this reason, a study conducted with wood extract of *K. malaccensis* stated that antimicrobial properties were observed due to the chemical structure of taxifolin found in wood extract [10]. Considering the studies in the literature, further studies were needed since the antimicrobial studies of taxifolin needed to be considered with MIC values or were not conducted with purified taxifolin. The synergistic effects between the compounds found in a wide variety of plant contents may also increase the biological activities of the plants. For this reason, other non-antimicrobial compounds found in small amounts in some trees may increase the antibacterial properties with the synergistic effect they create [22]. Therefore, antimicrobial studies conducted with plant extracts containing taxifolin may not yield reliable results due to the synergistic effects it may have with other compounds contained in the plant. For this reason, it is important to study taxifolin individually, independently of plant extracts.

In this study, taxifolin was found to have strong antibacterial and antifungal activities. When the results were detailed, taxifolin showed the most potent inhibitory activity against the Gram-positive microorganisms *S. aureus* and *E. aerogenes*, with a 1 mg/mL MIC value. After Gram positives, the MIC value of taxifolin against *P. aeruginosa*, *K. pneumonia*, and *E. coli*, among the Gram-negative microorganisms tested, was determined as 2 mg/mL. As a result of antifungal studies, *C. glabrata* (MIC: 4mg/mL) was slightly more sensitive to taxifolin than other *Candida* species (MICs: 8mg/mL). These results indicate bacterial cells are more sensitive to taxifolin than fungal cells, and these results may be attributed to the structural difference between bacterial and fungal cells. Consequently, taxifolin, a nutraceutical compound with proven medical value, should be evaluated for its usability in the treatment of infectious diseases due to its antimicrobial properties, and this valuable possibility should be supported by further *in vivo* studies.

Conclusion

The present work presents interesting scientific data on the potential of pure taxifolin in managing infectious disease results from opportunistic and pathogenic microorganisms. Antimicrobial studies also supported the action of taxifolin against the microorganisms tested, thus advocating further investigation geared towards assessing the antimicrobial properties of taxifolin. According to the test results, taxifolin showed a stronger inhibitory effect against Gram-positive microorganisms than other microorganisms, followed by Gram-negative and *Candida* species. Therefore, considering the potential pharmaceutical and health impact of taxifolin on human nutrition, both *in vivo* and bioavailability studies appear to be strongly needed to further support the preliminary data collected in this study.

Acknowledgment

This research was supported by the Research Fund of Inonu University (Project no TSA-2022-3110).

Ethical approval

Ethics committee permission is not required for this study.

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