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Evaluation of antioxidant, cytotoxicity and antimicrobial effects of *Achillea millefolium* (yarrow) and determination of phytochemicals

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Abstract

Achillea millefolium (*A. millefolium*) is one of the medicinal plants growing naturally in Anatolia and widely used in the treatment of many diseases, especially infectious diseases and digestive diseases. In this study, the determination of phenolic compounds, antioxidant, cytotoxic, and antimicrobial effects of plant extract of traditional *A. millefolium* were investigated. Phenolic compound analysis of the extract of the yarrow plant obtained with methanol was carried out by liquid chromatography-electrospray ionization-tandem mass spectrometry (LC–ESI–MS/MS). Antimicrobial effect was determined by the minimum inhibitory concentration (MIC) method and cytotoxicity analyses were carried out on androgen-dependent prostate cancer cells (LNCaP), human embryonic kidney 293 cancer cell lines (HEK293), and colorectal adenocarcinoma (CaCO-2) cell lines by the MTT method. Total antioxidant capacity was determined by the DPPH free radical scavenging activity determination method. In the determination of antimicrobial activity, it was tested on gram-positive *Bacillus subtilis* (*B. subtilis.*), gram-negative *Escherichia coli* (*E.Coli*) and *Candida albicans* (*C. albicans*) fungi. Among total phenolics, chlorogenic acid, caffeic acid, and salicylic acid were detected in high amounts. In the tests, the highest cytotoxic effect was shown on the LNCaP cell line, and the highest antimicrobial effect was shown on *B. subtilis.*

Keywords: *Achillea millefolium*, antioxidant, cytotoxic effect, antimicrobial

Introduction

Excessive levels of reactive oxygen species in the body are among the most important causes of cancer, neurodegenerative diseases and aging. Loss of oxidant/antioxidant balance in the cell results in the dominance of oxidative stress. Subsequently, many intracellular molecules, including DNA, RNA, lipids, and proteins, are damaged and changed, causing nicks in the DNA and defects in the DNA repair mechanism. Studies have demonstrated the role of oxidative stress and oxidative damage in the initiation and progression of cancer [1]. Cancer is among the leading health problems all over the world in terms of mortality and morbidity rates. It is the second most common type of disease after cardiovascular diseases. Cancer is the transformation of a healthy somatic cell into a diseased cell structure that can get out of control, escape from apoptosis, gain the ability to divide infinitely, and cause death [2]. Classical treatments have been used in cancer treatment so far, and various successes have been achieved. Among these treatments, we can count chemotherapy, proven surgery,

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radiotherapy, and immunotherapy, which have just begun to become widespread. An effective cancer treatment should prevent tumor development and metastasis. Medicinal herbal treatments, which have proven cytotoxic, anti-inflammatory, and anti-cancer effects in recent decades, can be used to increase a person's resistance to cancer or as an adjunct to chemotherapy [3].

When plants are exposed to nature's abiotic stress, it causes an increase in phenol production through shikimate and phenylpropanoid metabolic pathways to ensure the survival of the plant and increase its resistance to stress. These phenolic compounds are important for their free radical-scavenging and antioxidant properties. Medicinal plants are very rich in these bioactive compounds [4]. These bioactive compounds and their derivatives synthesized in medicinal plants have the capacity to increase therapeutic efficacy and reduce complications in patients with cardiovascular, infectious diseases, and cancer. Some of these plant phytochemicals are compounds naturally synthesized by the plant for defensive purposes, with significant anticancer and antimicrobial effects. Bioactive compounds control molecular signaling pathways that play a role in cancer development or act by causing cancer cells to undergo apoptosis [5]. Some of these compounds increase antibody synthesis in defense cells, strengthen cell-mediated immune responses, and may help in cancer treatments by preventing teratogenic and/or oncogenic effects [6].

A. millefolium is a plant from the *Asteraceae* (*Compositae*) family and grows widely in the world in natural environments. It is a perennial herbaceous plant with a rhizome or cytolon, hairy leaves, yellow, pink, and dense flowers that can generally grow from 10 cm to 1 meter. It has been known since ancient times for its healing properties. It is a preferred plant for respiratory tract infections, skin care and healing, stopping bleeding, ulceration treatments, and gastrointestinal system disorders [7]. It is rich in bioactive compounds and has an important place in folk medicine. Among the compounds obtained from the plant, phenolic acids, terpenes, phytoestrogens, phytosterols, fatty acids, organic acids, and alcohols have been shown [8]. Since the bioactive compounds contained in the plant are substances that provide hydrogen or electrons, they have the ability to reduce free radicals. Therefore, their chemical activities show potential for healing effects as free radical scavengers. It is now of great importance to know the properties of bioactive compounds in plants for nutrition and disease prevention, to benefit from their antioxidant properties, and to improve them. Although it is known that many *Achillea species* are used in folk medicine, there is limited information in the literature about the detailed chemical components and anticancer effects of the *A. millefolium* plant. The aim of this study is to investigate the bioactive compounds of *A. millefolium*, to evaluate its pharmacological properties, to investigate its effects on some important cell lines, and to determine the phytochemical content of the plant.

Material and Methods

Since our study is an in vitro laboratory study, ethics committee approval is not required.

Obtaining Yarrow (*A. millefolium*) Plant Extract and Analysis of Compounds

A. millefolium was collected from Iğdır in June and confirmed by Zafer Tel. It was then washed, cleaned, and stored in room conditions. The plants complete drying was turned into powder with a mixer. 200 g of powdered yarrow was weighed, and a solvent mixture of methanol and chloroform (1:1. 400 mL) was added and left for extraction under laboratory conditions for 14 days. After filtration, the solvents of the extracts were removed with an evaporator device at approximately 40–50°C. 100 mg of the obtained plant extract was taken and mixed until completely dissolved in 10 mL of methanol. After the solution was filtered through 0.45 mm filters, the solution was diluted with 50% aqueous methanol, and the analysis of the compounds in this aqueous solution was performed using the LC-ESI-MS/MS device [9].

Determination of Total Phenolic Substances

Using the Folin Ciocalteu (FCR) method discovered by Slinkard and Singleton [10], the amounts of total phenolic components in the yarrow plant extracts made with various solvents were ascertained. 4 mL of sodium carbonate solution (7.5%) and Folin Ciocalteu reagent (diluted 1/10) were added. Spectroscopy at 765 nm was used to quantify absorbance levels following a 20-minute incubation period at 25°C. For the calibration curve, a similar process was employed; the positive control was gallic acid, and the findings were reported as gallic acid equivalents (mg GAE/g extract).

Determination of the DPPH Free Radical Scavenging Activity Experiment

Plant samples were tested for antioxidant activity in accordance with Wu (2006) [11]. This technique's foundation is the spectrophotometric observation of the removal of oxidants and the distinctive purple hue of 2.2-diphenyl-1-picrylhydrazyl (DPPH), a persistent free radical, in the presence of antioxidant compounds that give hydrogen atoms and electrons. Initially, 1 ml (0.2–1.0 mg) extract solutions and 4 ml of 0.0004% (w/v) methanolic DPPH solution were combined, and absorbance values were determined at 517 nm following 30 minutes of incubation at room temperature in the dark. Using the samples' absorbance readings,

$$\%\text{inhibition} = \text{A control} - \text{A sample} / \text{A control} \times 100$$

Using the formula above, the percentage inhibition value was determined. The 50% inhibition (IC50) value was derived by plotting the obtained inhibition values against the extract concentrations, which were measured in milligrams per milliliter. This allowed for the calculation of the concentrations of each extract that produced 50% color lightening. BHA served as a positive control as well.

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Cell Culture and Cytotoxic Activities via the MTT Assay

The cytotoxic activities of yarrow plant extract on cells were performed according to the rapid, colorimetric, and quantitative MTT method as described previously [12]. The human androgen-dependent prostate cancer cell line (LNCaP), human colorectal adenocarcinoma cell line (CaCO-2), and human embryonic kidney cell line (HEK293) were sourced from the European Collection of Cell Cultures (ECACC). All three cell lines were cultured in Dulbecco's Modified Eagle Medium (DMEM), enriched with 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin solution. Cells were cultivated in a 100 mm culture dish within a humidified environment including 5% CO_2 at 37°C. Cells were subcultured every 2-3 days upon achieving 80% confluency.

Subsequent to passage, the cells were centrifuged at 2000 rpm for 5 minutes following the addition of fresh media, and the supernatant was discarded. Subsequently, 1 ml of fresh media was introduced to the plate, and the cells were enumerated using a light microscope utilizing Trypan Blue dye in conjunction with a Thoma slide. Aqueous extract was administered to all three cell lines at doses of 3.125, 6.25, 12.5, 25, 50, 62.5, and 125 µg/ml. Subsequently, the media in the wells was discarded, and 10 µl of MTT (3-(4.5-dimethylthiazol-2-yl)-2.5-diphenyltetrazolium bromide) reagent was introduced into each well. The formazan dye was subsequently dissolved in 50 µL of DMSO. The color intensity was quantified at 590 nm using a microplate reader (Epoch, BioTek, USA). All MTT assays were conducted in triplicate, and the cell survival rate was determined as a percentage of the control group. The obtained data were used for the calculation of the EC50 values. Calculations were performed by GraphPad Prism® software v.9 (San Diego, California, USA, "www.graphpad.com").

Antimicrobial Activity Determination

The antimicrobial effects of the *A. millefolium* plant extract we prepared on gram-negative and gram-positive bacterial strains and *Candida albicans* (*C. albicans*) fungus were examined using the microdilution method [13]. In practice, gram-positive *Bacillus subtilus*, ATTC 11774 (*B. subtilis*), which can form spores, and *Escherichia coli*, ATCC25922 (*E. coli*), which is a gram-negative bacillus, For positive control, vancomycin antibiotics were used for *B. subtilis*, colistin for the *E. coli* strain, and floconazole antibiotics for the *C. albicans* strain. The microorganisms used in the application were supplied from Artuklu University, İnönü University, and Dicle University, Türkiye. 96 microplate wells were used in the application. Suitable media for each strain were distributed into the wells. Extracts prepared at varying concentrations were distributed to the wells with a series of dilutions, starting from the first well. Some wells were used for growth and sterilization steps. Following these procedures, microorganisms prepared according to the McFarland 0.5 turbidity criterion were distributed into the wells. The same procedures were performed using the same method for an appropriate antibiotic for each strain (to compare the effect of the extract). Vancomycin antibiotics were used for gram-positive strains, colistin for gram-negative strains, and fluconazole antibiotics for yeast. The plates prepared to examine the antibiotic effects of microdilution were incubated in the oven at 25–37°C for 24 hours. Then, growth control was performed, and the minimum inhibitory concentration (MIC) was determined.

Statistical Analysis

Statistical analyses were performed using Graphpad Prism 6. All results are expressed as means with standard deviations (SD). Multiple comparisons were made to create graphs in the analyses and One-way ANOVA was used.

Results

Phytochemical Analysis of Yarrow (*A. millefolium*) Plant Extract

Phytochemical analyses of the plant were carried out by the LC-MS/MS method. Significant levels of compounds were detected in the plant extract. Phytochemical analyses of the plant were performed by the LC-MS/MS method. Significant levels of bioactive compounds were detected in the plant extract. According to the analysis results, it was determined that one gram of the plant extract contained chlorogenic acid in the highest order, caffeic acid in the second place, and salicylic acid in the third place. In addition to these compounds, trans-ferulic acid, trans-cinnamic acid, quercetin, naringenin, p-coumaric acid, isoquercitrin, protocatechuic acid, and 4-hydroxybenzaldehyde were found, respectively. (Figure 1 and Table 1).

Using the LC-MS/MS method, the compounds in Table 1 were screened and determined to have a high amount of chlorogenic acid (458.001 µg/g). In addition, the chromatogram of other compounds is given in Figure 1, and the quantitative results are given in Table 1. Chlorogenic acid, coumaric acid, caffeic acid, and ferulic acid, which we found in high amounts in the *A. millefolium* plant analysis, are derivatives of hydroxycinnamic acid. These bioactive compounds have strong antioxidant and anti-inflammatory antimicrobial properties, hence their importance in health [14]. Salomon et al. similarly detected chlorogenic acid and quercetin derivatives in the ethyl acetate extract of the *A. millefolium* plant. It has also been determined that high levels of chlorogenic acid are found in all species of plants. [15,16]. Likewise, Vitalini and his colleagues detected high amounts of chlorogenic acid in their analysis of methanol extract from the *A. millefolium* plant [17].

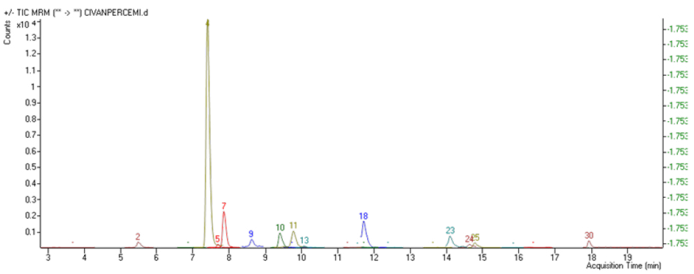

Figure 1. Multiple reaction monitoring (MRM) chromatogram of yarrow (*A. millefolium*) plant extract using the LC-MS/MS method

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Table 1. Analysis of the components of methanol and ethanol extracts from *A. millefolium* by LC–MS/MS

No	Compounds	RT	Yarrow (*A. millefolium*) (µg/g)
1	Chlorogenic acid	7.330	458.001
2	Caffeic acid	7.798	41.797
3	Salicylic acid	9.539	39.285
4	Trans-ferulic acid	10.132	21.151
5	Trans-cinnamic acid	14.272	20.679
6	Quercetin	14.644	16.736
7	Naringenin	14.999	15.687
8	p-coumaric acid	9.441	12.058
9	Isoquercitrin	11.851	10.458
10	Protocatechuic acid	5.409	9.710
11	Vanillin	8.649	4.809
12	4-Hydroxybenzaldehyde	7.679	2.840
13	Chrysin	17.963	0.426

Antioxidant Activity of Yarrow (*A. millefolium*) Plant Extract

In the data obtained at the end of the studies, it was observed that the increase in the amount of yarrow extract proportionally increased the number of antioxidants in the antioxidant capacity determination made by the DPPH and CUPRAC methods (Table 2). The only reason for this phenomenon may be the many free groups contained in the fruit, such as phenolic compounds with antioxidant effects. *A. millefolium* plant extract was found to have remarkable radical scavenging activity in antioxidant capacity measurement by both the DPPH and CUPRAC methods, and the fact that the total phenolic content of *A. millefolium* plant extract was found to be very high supports our findings that this activity may be due to its high bioactive phenolic compounds.

Table 2. DPPH free radical scavenging activity results (%) and CUPRAC (Copper (II) ion reduction capacity) experiment results

Examples	% value
A. millefolium (DPPH)	8.61±0.211
BHA	76.18±1.98
A. millefolium (CUPRAC)	32.78±0.641

BHA 0.04 mg/mL; other extracts are results at 1 mg/mL concentration, extracts are obtained at a concentration of 1 mg/mL

Total Phenolic Content Measurement Experiment Results

Achillea species have a rich complex of biologically active compounds. In recent years, *Achillea species* have attracted increasing attention for their antioxidant properties. For the antioxidant activity of *A. millefolium*, it was examined in vitro whether there was a relationship between its total phenolic content and antioxidant effect by undergoing certain processes. For the applicability of this study, *A. millefolium* extracts were prepared before measuring the antioxidant activity value. A special reagent, the 'Folin-Ciocalteau' method, was used to indicate the connection between antioxidant activity and yarrow phenolic content.

The gallic acid standard curve, which is necessary for the calculations to be made in determining the total phenolic substance amounts in yarrow extract, was used. This graph is given in Table 3. In creating standard curves, the equations defining the curves were determined from the data obtained in the analysis.

Table 3. Total phenolic substance amount of the samples in terms of gallic acid

Total phenolic substance amounts (mg GAE/g)		Gallic acid standard calibration equation	R2
A. millefolium	16.34±0.146	y = 0.0048x + 0.0009	0.9964

Cytotoxic Activity of CaCO-2 (*A. millefolium*)

In our cytotoxic study, *A. millefolium* extract was applied to LNCaP, HEK293 and CaC0-2 cell lines at concentrations of 3.125, 6.25, 12.5, 25 50, 62.5, and 125 µg/mL, respectively. LC-MS/MS analysis showed that *A. millefolium* extract, which we showed to have a structurally rich phenolic compound content, effectively inhibited the growth of cells and led them to the apoptotic process in human cancer cell lines. The best cytotoxicity results for all three cell lines were obtained at concentrations of 125 µg/ml (Figure 2). The extract showed its cytotoxic effect best at a concentration of 125 µg/mL in the LNCaP cell line. Later, a second-degree cytotoxic effect was shown in the CaCO-2 cell line at a concentration of 125 µg/mL of the plant extract.

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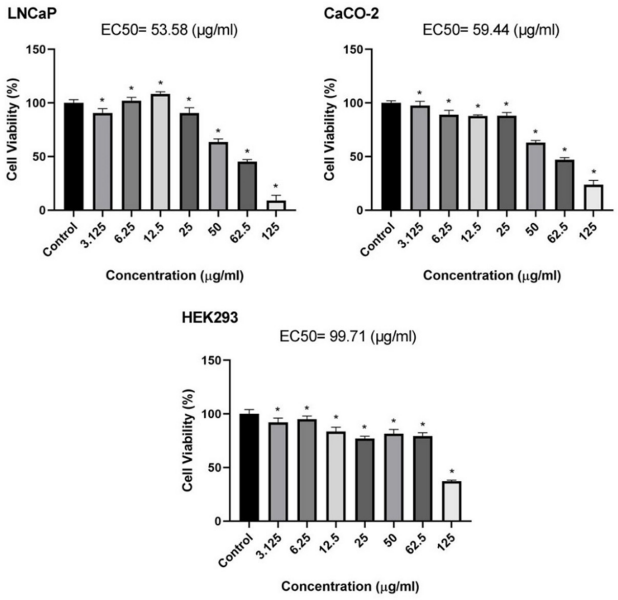

Figure 2. Anti-cancer activity of Yarrow (*A. millefolium*) plant extract

Antimicrobial Effect of the *A. millefolium* Plant

The antimicrobial effect of yarrow plant extract was tested on gram-negative *E. coli*, gram-positive *B. subtilis*, and *C. albicans* fungi by the microdilution method. As a result of the test, yarrow extract was highly effective on gram-positive *B. subtilis*, moderately effective on gram-negative *E. coli*, and had no effect on the *C. albicans* fungus (Table 4).

Table 4. Antimicrobial effect of *A. millefolium* plant extract

Organism	*A. millefolium* (mg/mL)	Antibiotic (ppm)
***E. coli* (ATCC25922)**	3.125	4
***B. subtilis* (ATCC 11774)**	0.162	2
C. albicans	3.125	1

Experimental conditions were made with 100 ppm (initial concentration)

Discussion

In our study, it was shown that the amount of total phenolic compounds in *A. millefolium* plant leaves was high. Among the total phenolics, the amounts of chlorogenic acid, caffeic acid, and salicylic acid were clearly detected. Sabanoğlu et al. In their study, they found a high amount of chlorogenic acid, dominantly in *A. millefolium species* [18]. Chlorogenic acid (CGA), identified at the highest concentration in the LC-MS/MS analysis of the *A. millefolium* plant, is a water-soluble polyphenolic molecule synthesized via the shikimic acid pathway. CGA exhibits significant biological and pharmacological effects, notwithstanding its poor bioavailability when derived from dietary sources. It is a naturally occurring non-flavonoid polyphenol with predominant antibacterial, antiviral, anti-inflammatory, antioxidant, and anticancer properties, along with renal, cardiovascular, and hepatic protective effects as lipid metabolism regulators. The biological functions of CGAs are contingent upon the body's pH, as well as the stability of temperature and light [19]. The chemical we examined at the second height in the *A. millefolium* plant is caffeic acid. This substance is classified as a polyphenol and is part of the hydroxycinnamic acids subgroup within the polyphenol category. Caffeic acid is typically present in plants as the ester of chlorogenic acid [20]. Caffeic acid's health-promoting properties stem mostly from its antioxidant properties. This feature results from the presence of two hydroxyl groups in caffeic acid's aromatic ring, which allows it to contribute hydrogen and stabilize the phenoxyl radical that finally forms [14]. Caffeic acid and its derivatives play an essential role in drug discovery since they exhibit a variety of pharmacological properties. Caffeic acid aids in the elimination of free radicals in the body and protects cells and tissues from wear and tear. Studies have shown that it has a variety of biological actions in human health, including antioxidant, anticancer, antiviral, antibacterial, anti-inflammatory, antidiabetic, and neuroprotective properties [16, 21-23]. Many researchers have identified significant quantities of bioactive compounds, including chlorogenic acid, caffeic acid, and quercetin, in the *Achillea species*, as demonstrated in our study [24-26]. The bioactive compound we determined to be the third most concentrated in the plant is salicylic acid. Salicylic acid is a significant phenolic signaling biomolecule and a plant hormone that plays a crucial role in plant growth, metabolism, and defense mechanisms against pathogens. It has an important role in strengthening the plant's defense system [27]. Salicylic acid has beneficial effects not only on plant health but also on human health. This bioactive plant hormone exhibits various properties beneficial to human health, including antidiabetic, anti-inflammatory, anticancer, neuroprotective, antineoplastic, antiviral, antiemetic, and anticonvulsant effects [28].

Bioactive compounds, phenolic acids, flavonoids, etc. It can be classified in various ways, such as. It is known that phenolic compounds are very effective scavengers of free radicals, most of which have oxidizing properties [29]. Our results show that the bioactive compounds of the plant may be the compounds that make the biggest contribution to the radical scavenging activity of *A. millefolium* extracts. investigated the total phenolic contents of two different *Achillea species* in methanol extracts using different extraction methods and showed that the total phenolic contents of the species were very close to our findings [30].

Chlorogenic acid is a phenolic compound formed by an ester bond between caffeic acid and quinic acid and is found in high amounts in most foods. Chlorogenic acid is also of great importance for human health as it has strong antioxidant and anti-inflammatory properties. Most studies conducted in recent years have shown that chlorogenic acid also plays a role in

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tumor development and prevention [31,32]. We showed that chlorogenic acid, cafeic acid, and salicylic acid are abundant in the *A. millefolium* plant. This strengthens the idea that the antitumor effect is mediated by these compounds. It is estimated that caffeic and chlorogenic acids exert their antitumor effects by modulating gene-specific DNA methylation in the cell [33]. In cancer cells, cell proliferation, adhesion, and invasion abilities are inhibited by bioactive compounds called phenolics. Simultaneously, these compounds prevent cell aggressivity, neoplasm transformation, and carcinogenesis from occurring. In other words, it has an antiproliferative effect. The neoplasmically transformed cell is directed to death by apoptotic mechanisms [34]. Compounds such as chlorogenic acid, caffeic acid, and salicylic acid, which are abundant in the *A. millefolium* plant and which we also showed to be present in high amounts in the plant in our study, have been shown to have very effective cytotoxic activity [33,35]. Ullah et al. showed that in their cytotoxicity experiments with Achillea fragrantissima plant extract cytotoxicity applications, it led the cell to apoptosis, especially in the LNCaP cell, supporting our study in their analysis on prostate cancer cells [36] Similarly, Sabbar et al. showed a dose-dependent cytotoxic effect in the LNCaP cell line in their anticancer studies on the *Achillea aleppica species* [37].

Grigore et al.'s findings in their antimicrobial activity experiments on A.millefolium are compatible with our test [38]. The aforementioned researchers also report high antimicrobial activity, especially in gram-negative bacteria, and good or moderate effectiveness in gram-positive bacteria [39]. They could not find an antifungal effect on the *C. albicans* mushroom.

Conclusion

Our research has uncovered novel insights regarding the yarrow plant, which holds significant medicinal value in the context of Anatolia. The investigation into the methanol extract of the plant has revealed a significant presence of bioactive compounds, notably chlorogenic acid and caffeic acid. Furthermore, the antioxidant capacity of these compounds is substantial, correlating with the plant's richness in phenolic compounds. Our research demonstrated that the plant exhibits antimicrobial properties against pathogens and cytotoxic effects on neoplastic cells, indicating its potential application in cancer treatment. Our research has demonstrated that the plant exhibits antimicrobial properties against pathogens and cytotoxic effects on neoplastic cells, indicating its potential application in cancer therapy. The observed effects can be attributed to the elevated levels of chlorogenic acid and caffeic acid, both of which are abundant in phenolic compounds within the plant. Considering the research done so far, yarrow has a significant antioxidant and radical-scavenging effect. For this reason, the plant, which is frequently used in Anatolian folk medicine and whose effects have been shown, is a candidate for further medical studies, and more research is needed on it.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
Since our study is an in vitro laboratory study, ethics committee approval is not required.

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