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Determination of optimum extraction conditions and evaluation of biological activities of *Prunus Armeniaca* L. (Apricot) fruit

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In this study, optimization and biological activities of biologically active components obtained from *Prunus armeniaca* L. (apricot) fruit were investigated. Within the scope of the study, optimum extraction conditions were determined by using different extraction parameters (temperature, time and ethanol/water ratio) and the most suitable extracts were produced in terms of biological activity. Response Surface Method (RSM) and Artificial Neural Networks-GENetic Algorithms (ANN-GA) techniques were applied for extraction optimization. Antioxidant, antiproliferative and anticholinesterase activities of the extracts obtained under optimum conditions were evaluated. In antioxidant activity tests, it was observed that the extracts optimized by ANN-GA method presented higher values in terms of total antioxidant status (TAS) and DPPH free radical scavenging activity. Likewise, it was determined that total phenolic and flavonoid contents of the extracts obtained by ANN-GA method were higher compared to the extracts obtained by RSM method. In antiproliferative activity tests, cytotoxic effects of optimized extracts on A549 lung cancer cell line were investigated and it was seen that they suppressed cell viability in a dose-dependent manner. It was found that extracts optimized by ANN-GA method showed stronger antiproliferative effect than extracts obtained by RSM method at certain concentrations. In anticholinesterase activity analyses, it was determined that extracts optimized by ANN-GA method had higher potential to inhibit acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes than extracts obtained by RSM method. However, when compared to galantamine used as reference inhibitor, it was found that the inhibitory effect of the obtained extracts was lower. As a result of phenolic component analysis, it was seen that extracts optimized by ANN-GA method had higher concentrations of phenolic components such as kaempferol, fumaric acid, gallic acid, caffeic acid and naringenin. However, it was found that some compounds (e.g. resveratrol and salicylic acid) were extracted at higher rates with the RSM method. In conclusion, the ANN-GA method increases the extraction efficiency of biologically active components of *P. armeniaca* fruit, strengthening their antioxidant, antiproliferative and anticholinesterase activities. These findings indicate that AI-supported extraction methods have the potential to be used in functional food and pharmaceutical applications.

Keywords Prunus armeniaca, Extraction optimization, Artificial neural networks, Antioxidant activity, Antiproliferative effect, Anticholinesterase activity, Phenolic compounds

Medicinal plants contain biologically active compounds that provide various health benefits and have attracted growing attention in recent scientific research[1]. *Prunus armeniaca* L., commonly known as apricot, is a

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valuable fruit species belonging to the Rosaceae family. Its fruits are rich in vitamins, minerals, and phenolic compounds, offering significant nutritional and therapeutic benefits. *P. armeniaca* has antioxidant, anti-inflammatory, antimicrobial, anticancer, hepatoprotective, cardioprotective and neuroprotective effects thanks to its biologically active components[2,3]. Being especially rich in β-carotene, vitamin C and polyphenols, it contributes to the prevention of chronic diseases by reducing oxidative stress caused by free radicals. Its anti-inflammatory effects allow it to be evaluated as a potential agent in the treatment of diseases associated with inflammation. In addition, considering that amygdalin, a cyanogenic glycoside, is found specifically in apricot seeds not the fruit. It is the seed consumption that should be limited due to potential toxicity[4]. Scientific research conducted in recent years has examined the biological activities of *P. armeniaca* in more detail, revealing its potential in medical and pharmaceutical applications. In addition to antioxidant and antiproliferative properties, inhibition of cholinesterase enzymes such as acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) has therapeutic relevance, particularly in the context of neurodegenerative diseases like Alzheimer's disease. Plant-derived cholinesterase inhibitors are of increasing interest as potential alternatives to synthetic drugs[5]. Therefore, AChE/BChE inhibition assays were included in this study to evaluate the possible neuroprotective potential of *P. armeniaca* fruit extracts. In our study, the optimum extraction conditions obtained from the fruit of *P. armeniaca*, which provide the highest biological activity, were determined. Then, the extracts were produced under these conditions and their biological potential was evaluated. A key innovative aspect of the present study is the use of an Artificial Neural Network-Genetic Algorithm (ANN-GA) model for optimizing extraction conditions. Unlike traditional extraction approaches based on fixed experimental designs or linear assumptions, ANN-GA can learn complex nonlinear relationships among variables and identify the global optimum with high precision[6]. Combined with RSM, this dual-optimization framework enables a more efficient, predictive, and data-driven extraction strategy that has not been previously applied to P. armeniaca fruit. Although several studies have optimized apricot fruit extracts using RSM mostly focusing on antioxidant activity or total phenolic content these investigations were limited to single-method optimization and did not include any artificial intelligence-based modeling approaches[7,8]. Similarly, other works on *P. armeniaca* have described its phytochemistry or biological activities, yet they did not perform extraction optimization nor evaluate different optimization strategies comparatively[9]. To the best of our knowledge, no previous study has applied an ANN-GA model to optimize extraction conditions for *P. armeniaca*, nor directly compared ANN-GA and RSM under identical experimental parameters. Furthermore, none of the earlier studies simultaneously assessed antioxidant, antiproliferative, anticholinesterase, and detailed phenolic composition of extracts produced under their respective optimal conditions. Therefore, the present study represents the first and most comprehensive attempt to integrate both RSM and ANN-GA for extraction optimization and to evaluate the resulting extracts across multiple biological activity platforms.

Materials and methods

The *P. armeniaca* fruits used in this study were obtained from Malatya province, Türkiye, and belonged to the 'Hacihaliloğlu' cultivar, which is the most widely cultivated and commercially important apricot variety in the region. The fruits were harvested in mid-July 2023, during the peak ripening season, at geographic coordinates 38.3552° N and 38.3095° E. A voucher specimen of the plant material was collected under the collector number MS-1816 and deposited in the Herbarium of the Department of Biology, Osmaniye Korkut Ata University, Osmaniye, Türkiye. Selection was based on typical maturity indicators such as fully developed orange skin color and adequate firmness. °Brix values were not measured. The harvest period was characterized by hot and dry summer conditions, with average daytime temperatures around 32 °C. After the seeds of the samples were carefully separated, the fruit drying process was carried out using a Dalle SS-06 A model dryer at 50 °C for approximately 6–8 h. After the drying process was completed, the dried fruit material obtained was ground into fine powder with a mechanical grinder. Then, extraction processes were applied on these powdered samples to be used in the analyses.

Extraction protocol

The development of the extraction protocol was based on a full factorial experimental design, which systematically investigated three primary factors: extraction temperature, extraction duration, and the ethanol/water ratio. Each of these factors was assessed across three distinct levels, necessitating the execution of twenty-seven individual experimental trials within a Soxhlet apparatus. The extraction temperatures were specifically chosen as 45 °C, 55 °C, and 65 °C; the durations as 5 h, 10 h, and 15 h; and the ethanol/water ratios as 0%, 50%, and 100%. Ethanol-water mixtures were chosen because they are safer, food-grade, and suitable for applications related to human use[10,11]. Although methanol can yield higher levels of some phenolics, its toxicity and regulatory limitations make it inappropriate for studies aimed at potential functional food or therapeutic applications[12]. Ethanol-water systems also provide efficient extraction of a broad range of polar phytochemicals[10,11]. Subsequently, the experimental data obtained were subjected to a comprehensive analysis and optimization process, employing Response Surface Methodology (RSM) alongside a sophisticated artificial intelligence framework that integrates Artificial Neural Networks (ANN) with Genetic Algorithms (GA). Although several biological parameters were evaluated in this study, TAS was selected as the primary response variable for the optimization process due to its strong correlation with antioxidant capacity and its relevance in preliminary screening of extract quality. Optimizing TAS serves as a reliable indicator of overall extract efficiency, especially in studies where multiple bioactivities are evaluated. Additionally, focusing on a single representative parameter allowed for a more manageable and statistically robust optimization model. Other parameters were subsequently evaluated using the extracts obtained under the optimized conditions.

Response surface methodology (RSM)

In this research, Response Surface Methodology (RSM) was employed as the optimization technique, with a focus on three independent variables, namely extraction temperature, extraction duration, and the ethanol/water ratio. The total antioxidant activity (TAS) value, derived from the extract, was selected and designated as the key response variable to be analyzed throughout the study.

Using Design Expert version 13.0.5.0 (Stat-Ease Inc., Minneapolis, MN, USA) software, the optimization process was carried out with a second-order polynomial response model, as described below.

$$Y_k = \beta_{k0} + \sum_{i=1}^{n} \beta_{ki} x_i + \sum_{i=1}^{n} \beta_{kii} x_i^2 + \sum_{i=1}^{n-1} \sum_{j=i+1}^{n} \beta_{kij} x_i x_j$$

where Y_k was response variable (Y_i was TAS value of extract); x_i was coded process variables (x_1 was extraction temperature, x_2 was extraction time, and x_3 was ethanol/water ratio) and β_{k0} is the value of fitted response at the design center point, respectively.

The suitability of the model was rigorously assessed through multiple statistical measures, including the coefficient of determination (R^2), analysis of variance (ANOVA), and associated p-values. To achieve optimization of the response variable, critical points were identified by computing the derivatives of the model. Additionally, three-dimensional surface plots were generated to provide a visual representation of the interactions among the independent variables, thereby facilitating a more detailed and comprehensive evaluation of their collective impact on the response.

ANN-GA

In this investigation, an Artificial Neural Network (ANN) (MATLAB, R2020b) methodology was implemented to develop a predictive model, incorporating extraction temperature, extraction duration, and the ethanol/water ratio as the input variables, while designating the total antioxidant activity (TAS) value as the output parameter. The dataset was systematically partitioned into three subsets: 80% allocated for training, 10% reserved for validation, and 10% utilized for testing purposes. The learning process was facilitated by the application of the Levenberg-Marquardt (LM) algorithm. To identify the most effective network architecture, a series of 20 different configurations of hidden neurons, ranging from 1 to 20, were meticulously evaluated. Key parameters were consistently maintained throughout the process, with the learning coefficient and momentum coefficient fixed at 0.5, the maximum number of iterations established at 500, the number of validation checks set at 50, and the error threshold defined as 1×10^{-5}. Each individual model underwent an extensive training regimen consisting of 1000 separate sessions.

The performance of the model was systematically assessed through the application of two key evaluation metrics: the mean square error (MSE) and the mean absolute percentage error (MAPE). These metrics were derived by employing the mathematical formulations outlined in the subsequent equations, specifically Eq. 1 for MSE and Eq. 2 for MAPE, as presented below.

$$\mathrm{MSE} = \frac{1}{\mathrm{n}} \sum_{\mathrm{i}=1}^{\mathrm{n}} (\mathrm{e_i} - \mathrm{p_i})^2 \tag{1}$$

$$\mathrm{MAPE} = \frac{1}{\mathrm{n}} \sum \left| \frac{\mathrm{e_i} - \mathrm{p_i}}{\mathrm{e_i}} \right| * 100 \tag{2}$$

where e is the experimental result, p is the prediction result, and n is the number of samples.

In the optimization process, the Genetic Algorithm (GA) was utilized as the primary computational approach. A range of population sizes was systematically explored to assess their impact, and the roulette wheel selection method was adopted to determine the individuals advancing to the next generation. For the crossover phase, the single-point crossover technique was consistently implemented. The most suitable number of iterations was established by carefully analyzing convergence graphs, which provided insight into the algorithm's performance. To ensure that the results approximated the global optimum as closely as possible, each optimization trial was conducted a minimum of 60 times.

Extraction for bioactivity

The most suitable extraction parameters predicted to show the highest biological activity were determined. According to RSM analysis, the optimum extraction conditions were determined as 54.353 °C temperature, 13.616 h extraction time and 41.236 ethanol/water ratio. As a result of the optimization studies conducted with the ANN-GA method, the most suitable conditions were determined as 57.057 °C temperature, 11.791 h extraction time and 64.899 ethanol/water ratio. These determined parameters were applied with computer support using the Gerhardt SOX-414 device and the biological activities of the obtained extracts were analyzed based on the extraction process performed under these conditions. To validate the predictive capability of the optimization model, the TAS value of the extract obtained under the determined optimal ANN-GA and RSM conditions was experimentally measured. The experimental TAS results showed a high agreement with the predicted values, confirming the accuracy and reliability of the developed models. Extraction yield (%) was not measured during the study. We acknowledge that extraction yield is a critical factor for assessing the economic feasibility and scalability of extraction processes. This represents a limitation of our work and will be considered in future studies to improve industrial applicability.

Antiproliferative activity

The antiproliferative effects of optimized extracts were analyzed on the A549 lung cancer cell line. The A549 cell line (human lung adenocarcinoma, ATCC® CCL-185™) used in this study was obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA). Cell line authentication was confirmed by short tandem repeat (STR) profiling prior to experimentation. To ensure experimental reproducibility and minimize genetic drift, all antiproliferative assays were conducted using cells between passages 5 and 15. For this purpose, stock solutions were prepared from the extracts at concentrations of 25, 50, 100 and 200 µg/mL. After the cells reached 70–80% confluency, 3.0 mL of Trypsin-EDTA solution (Sigma-Aldrich, MO, USA) was used to separate the cells from the culture surface and seeded onto appropriate plates. Following seeding, the cells were incubated for 24 h. Then, the prepared stock solutions were applied to the cells and an additional 24-hour incubation period was performed. After incubation was completed, the supernatants were removed and 1 mg/mL MTT solution was added and incubated at 37 °C until a purple precipitate formed. In the final stage, dimethyl sulfoxide (DMSO) (Sigma-Aldrich, MO, USA) was added to dissolve the precipitate and the absorbance values of the obtained solutions were measured using an Epoch spectrophotometer (BioTek Instruments, Winooska, VT) at 570 nm wavelength[13].

Antioxidant activity tests

Total antioxidant and oxidant analysis

Total antioxidant capacity measurements of optimized extracts of *P. armeniaca* fruit were performed using the Rel Assay TAS kit. Analysis results were expressed in mmol Trolox equivalent/L. Total oxidant levels were determined with the Rel Assay TOS kit and the results were reported in µmol hydrogen peroxide equivalent/L[14,15]. Oxidative stress index (OSI) calculations were performed by dividing the total oxidant capacity by the total antioxidant capacity and expressed as a percentage[16].

DPPH free radical scavenging activity

Stock solutions of optimized extracts were prepared by dissolving them in DMSO at a concentration of 1 mg/mL. 1 mL of this stock solution was taken and mixed with 160 µL of 0.267 mM DPPH solution. The DPPH solution was prepared in 4 mL of 0.004% methanol. The mixture was incubated at room temperature and in the dark for 30 min. After the incubator process, absorbance measurements were performed at a wavelength of 517 nm. The results were expressed in Trolox equivalents per extract (mg TE/g extract)[17].

Ferric reducing antioxidant power assay

100 µL stock solution was prepared from optimized extracts and mixed with 2 mL FRAP reagent. FRAP reagent was obtained by combining 300 mM acetate buffer (pH 3.6), 40 mM HCl and 20 mM $FeCl_3 \cdot 6\,H_2O$ solution with 10 mM 2,4,6-tris(2-pyridyl)-S-triazine solution at a ratio of 10:1:1. The mixture was incubated at 37 °C for 4 min. After the incubation process, absorbance measurement was performed at a wavelength of 593 nm. The results were expressed in mg Trolox Equivalent/g extract unit[17].

Total phenolic and total flavonoid methods

1 mL stock solution was prepared from the extracts obtained under optimum conditions. 1 mL of Folin-Ciocalteu reagent (1:9, v/v) was added to this solution and mixed well. Then, 0.75 mL of 1% Na_2CO_3 solution was added to the mixture and incubated for 2 h at room temperature. At the end of the period, absorbance measurement was performed at 760 nm wavelength. Total phenolic compound amount was calculated in mg/g based on gallic acid standard curve[18]. Total flavonoid levels of the extracts obtained under optimum conditions were determined by aluminum chloride test. For this purpose, 0.1 mL of 10% $Al(NO_3)_3$, 0.1 mL of 1 M NH_4CH_3COO, 4.3 mL of methanol, 0.5 mL of quercetin solution and 0.5 mL of plant extract were mixed. After the prepared mixture was incubated for 40 min, the absorbance value was measured at 415 nm wavelength. Total flavonoid content was expressed in mg/g[18].

Anticholinesterase activity tests

The anticholinesterase activities of optimized extracts were analyzed based on the Ellman method[19]. Galantamine was used as a reference inhibitor in the study. Stock solutions were prepared from the extracts at different concentrations ranging from 200 to 3.125 µg/mL. In the tests performed in microplate format for analysis, firstly 130 µL of 0.1 M pH = 8 phosphate buffer was added to each well. Then, 10 µL of extract solution and 20 µL of AChE or BChE enzyme solutions were added, respectively, and incubated for 10 minutes at 25°C in the dark. After the incubation period was completed, 20 µL of DTNB solution (5.5"-dithiobis-(2-nitrobenzoic acid)) and 20 µL of substrate (acetylcholine iodide or butyrylcholine iodide) were added to start the reaction, respectively. The absorbance values of the products formed as a result of the enzymatic reaction were measured at a wavelength of 412 nm. Enzyme inhibition rates were calculated in line with the obtained data and IC_{50} values (in µg/mL) were determined and reported.

Phenolic analysis

The phenolic compound profile of the optimized extracts was analyzed using the LC-MS/MS system. Within the scope of the study, 24 different standard phenolic compounds found in the extracts were screened. The separation of the compounds was carried out by means of a C-18 Intersil ODS-4 analytical column (3.0 mm × 100 mm, 2 µm) and the column temperature was fixed at 40 °C. Mobile phase A (water containing 0.1% formic acid) and mobile phase B (methanol containing 0.1% formic acid) were used for the separation process. During the analysis, the flow rate was determined as 0.3 mL/min and 2 µL of sample was loaded for each injection. The

LC-MS/MS method used in this study was validated in terms of linearity and detection capability. Calibration curves for 24 phenolic compounds showed high linearity, with R^2 values generally exceeding 0.998. The method included multiple concentration levels (5–750 ppb). LOD and LOQ values were determined for each compound based on calibration data and are reported in the results table. Although recovery and intra-/inter-day precision analyses were not conducted, this limitation is acknowledged in the discussion. Figure 1 shows the representative LC-MS/MS chromatogram of the phenolic standard mixture used in this study. Each compound was successfully separated, confirming the selectivity of the method and enabling accurate quantification of individual phenolics.

Statistical analyses

In this research, all statistical evaluations were performed utilizing the SPSS 21.0 software designed for the Windows operating system. To examine statistical differences between pairs of groups, the independent samples t-test was applied, whereas comparisons involving more than two groups were analyzed through the application of One-Way Analysis of Variance (ANOVA). Subsequently, Duncan's multiple range test, conducted at a confidence level of $\alpha = 0.05$, was employed to pinpoint statistically significant distinctions among the groups under investigation.

Results and discussions

Optimization of extraction conditions

This study explored how extraction temperature (45, 55, 65 °C), extraction time (5, 10, 15 h), and ethanol/water ratio (0%, 50%, 100%) affect total antioxidant activity (TAS). The TAS values derived from the extracts are presented in Table 1.

The results demonstrate that TAS values were maximized at 55 °C and 10 h of extraction, achieving 9.672 ± 0.035, 9.642 ± 0.027, and 9.610 ± 0.036 mmol/L at 0%, 50%, and 100% ethanol/water ratios, respectively, highlighting this as the optimal condition. At 45 °C, TAS ranged between 6.369 ± 0.041 mmol/L (15 h, 0% ethanol) and 7.331 ± 0.035 mmol/L (10 h, 100% ethanol), indicating stable but lower antioxidant activity. At 65 °C, TAS decreased significantly, with values from 5.835 ± 0.017 mmol/L (15 h, 0% ethanol) to 7.151 ± 0.038 mmol/L (10 h, 100% ethanol), suggesting heat-induced degradation. Extending extraction to 15 h reduced TAS across all temperatures, most notably at 65 °C. Ethanol concentration had little influence on peak TAS at 55 °C but moderated the decline at 65 °C, with 100% ethanol yielding slightly higher values than 0% or 50%.

In this investigation, two distinct optimization strategies were implemented based on the experimental dataset. Within the framework of Response Surface Methodology (RSM), a comprehensive evaluation was conducted, comparing linear, two-factor interaction (2FI), quadratic, and cubic regression models. The quadratic model

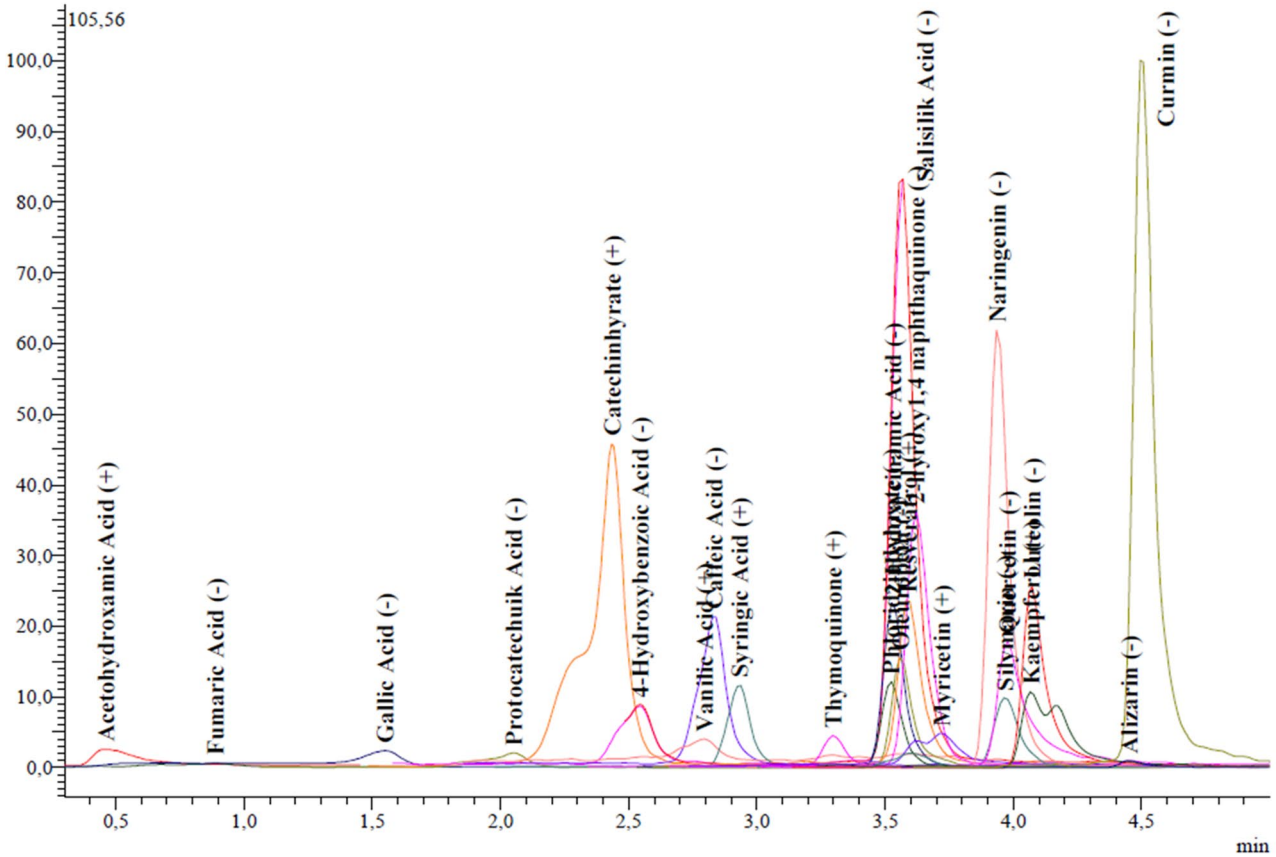

Fig. 1. LC-MS/MS phenolic standard chromatogram.

Experiment number	Extraction temperature (°C)	Extraction time (h)	Ethanol/water ratio (%)	TAS (mmol/L)
1	45	5	0	7.047 ± 0.077^{de}
2	45	10	0	7.297 ± 0.035^{h}
3	45	15	0	6.369 ± 0.041^{b}
4	45	5	50	7.031 ± 0.032^{d}
5	45	10	50	7.302 ± 0.026^{h}
6	45	15	50	6.430 ± 0.027^{b}
7	45	5	100	7.038 ± 0.058^{de}
8	45	10	100	7.331 ± 0.035^{h}
9	45	15	100	6.376 ± 0.031^{b}
10	55	5	0	8.018 ± 0.030^{i}
11	55	10	0	9.672 ± 0.035^{j}
12	55	15	0	7.096 ± 0.034^{defg}
13	55	5	50	8.139 ± 0.028^{i}
14	55	10	50	9.642 ± 0.027^{j}
15	55	15	50	7.080 ± 0.031^{def}
16	55	5	100	8.148 ± 0.031^{i}
17	55	10	100	9.610 ± 0.036^{j}
18	55	15	100	7.124 ± 0.039^{fg}
19	65	5	0	6.531 ± 0.010^{c}
20	65	10	0	7.138 ± 0.023^{fg}
21	65	15	0	5.835 ± 0.017^{a}
22	65	5	50	6.547 ± 0.036^{c}
23	65	10	50	7.148 ± 0.018^{g}
24	65	15	50	5.849 ± 0.025^{a}
25	65	5	100	6.554 ± 0.031^{c}
26	65	10	100	7.151 ± 0.038^{g}
27	65	15	100	5.852 ± 0.024^{a}

Table 1. The TAS values derived from the extracts.

was ultimately selected due to its superior coefficient of determination (R^2) value of 0.876, which quantifies the proportion of variance in the response variable accounted for by the independent variables. A high R^2 value signifies that the model robustly captures the underlying data patterns, thereby affirming its suitability for accurately delineating the relationships among the independent variables and providing dependable outcomes in the optimization process.

The quadratic polynomial equation, which was formulated through the application of multiple regression analysis to estimate the total antioxidant activity (TAS) values of *P. armeniaca*, is provided in the following expression.

$$TAS = 9.10 - 0.200\,X_1 + 0.006\,X_2 - 0.389\,X_3 + 0.001\,X_1X_2 - 0.012\,X_1X_3 - 0.003\,X_2X_3 - 1.59\,X_1^2 + 0.002\,X_2^2 - 1.19\,X_3^2$$

In the equation X_1, X_2 ve X_3 correspond to the extraction temperature, extraction time, and ethanol/water ratio, respectively.

The response surface plots, which visually depict TAS values of *P. armeniaca*, are illustrated and provided in Fig. 2. These plots were generated by the authors using Design Expert software (version 13.0.5.0, Stat-Ease Inc., Minneapolis, MN, USA) as part of the RSM-based optimization process.

Throughout the optimization process, which leveraged artificial intelligence techniques, an Artificial Neural Network (ANN) was employed to model the experimental dataset. Subsequently, the highest-performing model underwent further enhancement through the application of a Genetic Algorithm (GA). The optimal predictive model, characterized by a 3-46-1 architecture featuring six hidden neurons, was identified and chosen due to its remarkable precision, as evidenced by a mean square error (MSE) of 0.002, a mean absolute percentage error (MAPE) of 0.379%, and a correlation coefficient (R) of 0.999.

In this study, the Genetic Algorithm (GA) was utilized to perform optimization based on the highest-performing Artificial Neural Network (ANN) model. Following an evaluation of different population sizes, a value of 10 was determined to be the most suitable for achieving effective results. The convergence graph, presented in Fig. 3, provides visual evidence that the chosen number of iterations, specifically 20, was sufficient to ensure convergence and stabilize the optimization process.

Antiproliferative activity

Plants rich in bioactive components contain natural compounds that can play an important role in the treatment of serious diseases such as cancer. Phytochemicals, especially polyphenols, flavonoids, alkaloids, and terpenoids,

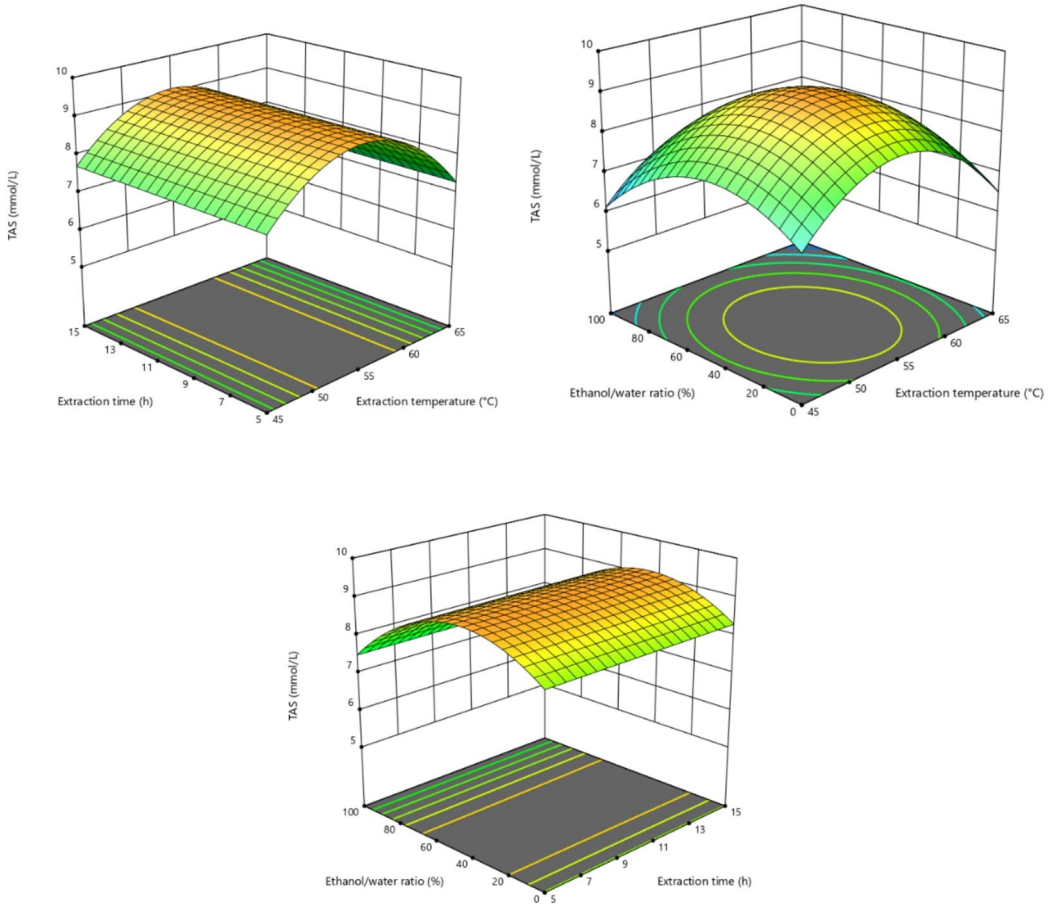

Fig. 2. Response surface plots of TAS of *Prunus armeniaca*.

can suppress tumor growth by regulating cell division[20,21]. These components can prevent the proliferation of cancer cells by exhibiting antiproliferative activity through mechanisms such as induction of apoptosis, reduction of oxidative stress, and control of the cell cycle. Scientific studies conducted in recent years have revealed that plant-derived bioactive components can be considered as potential alternatives to chemotherapeutic agents and contribute to the development of new approaches based on plant components in cancer treatment[22]. In our study, the activity of the optimized extract obtained from the fruit of *P. armeniaca* against the A549 lung cancer cell line was determined. The findings are shown in Fig. 4.

Our study demonstrates the antiproliferative effect of optimized extracts obtained from *P. armeniaca* fruit on A549 lung cancer cell line. Extracts optimized with RSM and ANN-GA methods were applied at different concentrations (25, 50, 100 and 200 µg/mL) and their effects on cell viability were evaluated by MTT test. The findings show that both extracts suppressed cell proliferation dose-dependently. While no significant decrease in cell viability was observed in the control and DMSO groups, a significant inhibition occurred in the extract-applied groups, especially at concentrations of 100 and 200 µg/mL. Although there was no visible difference between the extracts optimized with RSM and ANN-GA methods, it is noteworthy that ANN-GA extract may have a slightly stronger antiproliferative effect at some concentrations. This suggests that ANN-GA method may have provided more efficient extraction of bioactive components. It has been reported in the literature that ethanol extracts of *P. armeniaca* exhibit strong cytotoxic effects on the A549 cell line. In particular, it was reported in the study that ethanol extract applied at a dry matter concentration of 4 mg/mL showed 88.2% cytotoxicity in A549 cells[23]. Although the concentrations used in our current study were lower, the findings obtained support these literature data. The observation of a significant antiproliferative effect at lower concentrations reveals the effective role of phenolic and flavonoid compounds in the optimized extracts on cancer cells. However, since the studies in the literature are generally carried out using different extraction methods and solvents, different results can be obtained in terms of bioactive compound profile and bioavailability. For example, while ethanol extracts can dissolve hydrophobic compounds more effectively[24], the optimized extracts in the current study were obtained by methods using water and ethanol at certain ratios. Therefore, factors such as extraction protocol, solvent type, and chemical content of plant material may directly affect the effect of the extract on cells.

In conclusion, this study demonstrates that *P. armeniaca* exhibits antiproliferative activity in the A549 lung cancer cell line and this effect increases dose-dependently. Compared to the strong cytotoxic effects reported in the literature[23], the ability of optimized extracts to inhibit cell growth even at lower concentrations indicates that

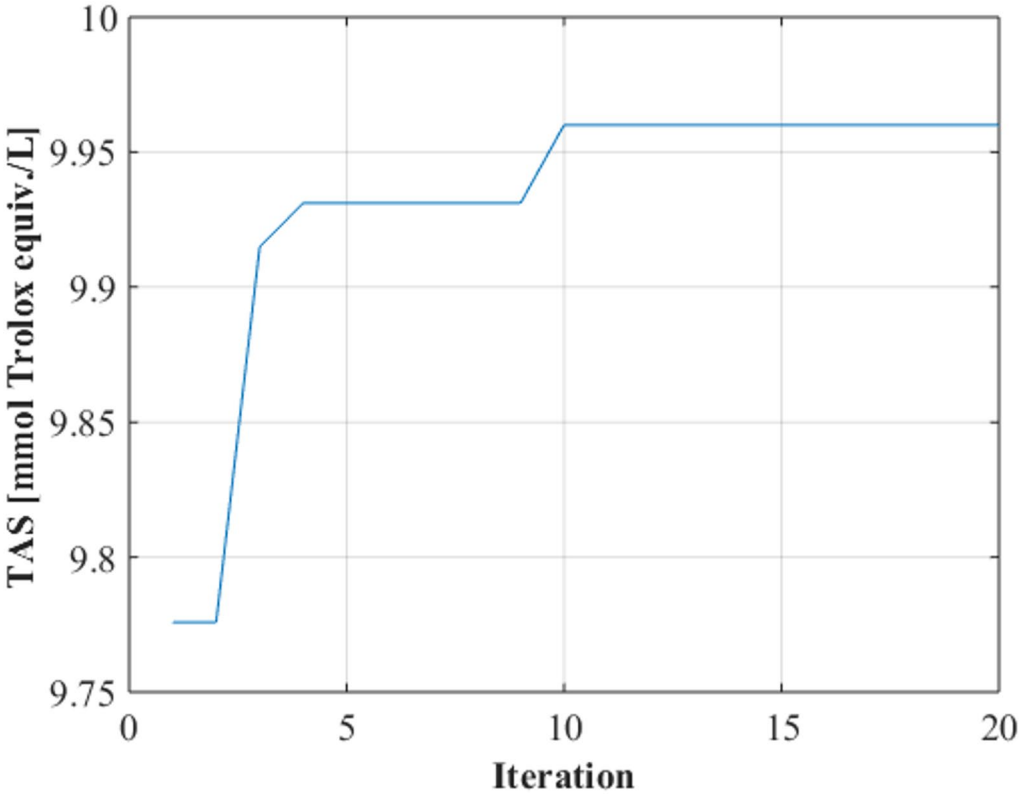

Fig. 3. Convergence graph of optimization process.

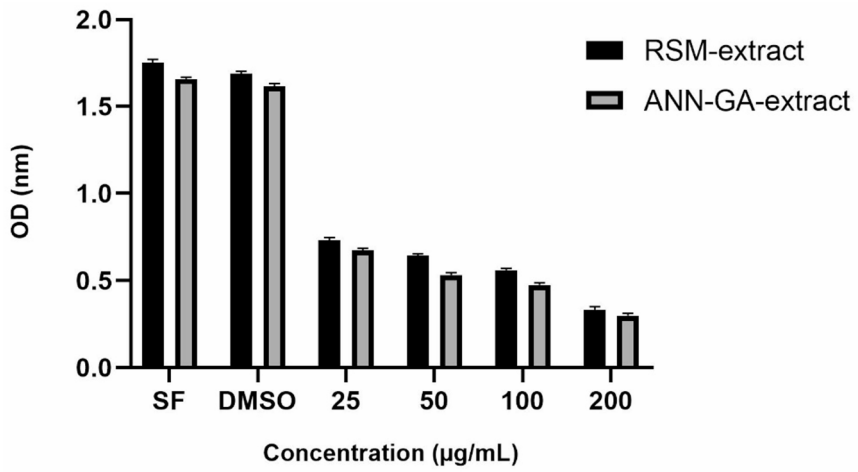

Fig. 4. Antiproliferative activity of *P. armeniaca* fruit extracts. (RSM: extract optimized using Response Surface Methodology; ANN-GA: extract optimized using the Artificial Neural Network–Genetic Algorithm model. SF (Control group): Cells cultured in standard growth medium without any treatment. DMSO group: Cells exposed only to DMSO (solvent control) without extract application. Extract-treated groups: Cells treated with extracts at concentrations of 25, 50, 100, and 200 µg/mL)

these extracts have potential as phytotherapeutic agents in cancer treatment. However, for a better understanding of the mechanism, the effects on apoptosis, cell cycle, and oxidative stress pathways should be examined in detail.

Antioxidant activity

Antioxidant activity refers to biochemical mechanisms that reduce oxidative stress caused by free radicals in cells. Oxidative stress is a condition that damages cells as a result of the accumulation of free radicals and reactive oxygen species in the body[25]. Plants are rich in natural antioxidant compounds and contain substances such as

phenolic compounds, flavonoids, carotenoids, and vitamin C. These compounds prevent cellular damage by neutralizing free radicals and can protect against various diseases. Therefore, plant-derived antioxidants are both important for health and valuable in terms of natural treatment and protection methods[26]. In our study, the antioxidant potentials of optimized extracts of *P. armeniaca* fruit were determined. The findings are shown in Table 2.

In our study, antioxidant parameters obtained from *P. armeniaca* fruit are presented comparatively. When the antioxidant capacities of the samples extracted by RSM and ANN-GA methods were evaluated, it was seen that the extracts obtained by ANN-GA method generally had higher antioxidant capacity. In terms of DPPH radical scavenging capacity, it was determined that the samples extracted by ANN-GA method showed higher values with 208.72 ± 1.42 mg Trolox Equi/g than the samples obtained by RSM method (188.89 ± 2.02 mg Trolox Equi/g). Similarly, iron reducing power (FRAP) was measured as 294.88 ± 2.15 mg Trolox Equi/g in the samples obtained by ANN-GA method, while it was 267.03 ± 1.66 mg Trolox Equi/g in RSM extracts. These findings show that the ANN-GA method can increase the extraction efficiency of polyphenols and antioxidant components. When evaluated in terms of OSI, it was determined that ANN-GA extracts were lower than RSM extracts (0.065 ± 0.001) with a value of 0.052 ± 0.001. This suggests that the samples obtained with the ANN-GA method may be more advantageous in terms of oxidative balance. In parallel with this result, TOS levels were measured as 5.176 ± 0.032 µmol/L in samples extracted with the ANN-GA method and 6.242 ± 0.034 µmol/L in samples obtained with the RSM method. On the other hand, TAS levels were found as 10.042 ± 0.035 mmol/L with the ANN-GA method and 9.560 ± 0.022 mmol/L with the RSM method. The fact that ANN-GA extracts have lower oxidant levels and higher antioxidant capacity indicates that this method may be more effective in preserving biologically active components. In the literature, it has been reported that the fruit of *P. armeniaca* has antioxidant activity using different methods[27–29]. These studies support the strong antioxidant potential of *P. armeniaca* fruit and show that different extraction methods can be a determining factor on the amount and effectiveness of antioxidant components. In the current study, it is seen that the ANN-GA method increases the antioxidant capacity of *P. armeniaca* by providing a more effective extraction compared to other traditional methods reported in the literature. In addition, the TPC and TFC contents of *P. armeniaca* fruit were determined. While the TPC values obtained in our study ranged between 662.480 ± 1.931 and 705.967 ± 2.350 mg GAEqui/g, the TFC values were found to be between 361.660 ± 1.168 and 386.173 ± 2.134 mg QEEqui/g. When compared with the studies in the literature, it was reported that the total phenolic content of *P. armeniaca* fruit was between 241.1 and 434.1 mg/g and the total flavonoid content was between 80.0 and 139.0 mg/g[30].

The TPC and TFC values obtained in our study are significantly higher than the values reported in the literature. This difference may be due to the variability in the extraction methods, solvents used, ecological conditions where the fruit is grown, ripening status and analysis methods. In particular, the extraction efficiency of phenolic and flavonoid compounds may vary significantly depending on the method and solvent system used. In addition, the extraction method and conditions used in our study may have provided more efficient extraction of phenolic compounds.

The high TPC and TFC values obtained in our study indicate that *P. armeniaca* fruit is quite rich in phenolic and flavonoid content and therefore may have high antioxidant capacity. However, the fact that these values are significantly higher than those reported in the literature may be due to differences in extraction methods, solvent selection, growing conditions and analysis methods. Therefore, in order to better understand the obtained results, comparison of different extraction methods, detailed profiling of phenolic components and bioavailability studies should be carried out. In particular, the ANN-GA method used in our study showed superior performance compared to the traditional RSM method in both increasing antioxidant capacity and reducing oxidative stress levels. This finding reveals that artificial intelligence-supported optimization methods can increase extraction efficiency and provide more biologically effective extracts. In conclusion, it is of great importance to evaluate alternative extraction techniques to increase the bioavailability of functional food ingredients such as *Prunus armeniaca* and maximize their antioxidant potential.

Anticholinesterase activity

Anticholinesterase activity is a mechanism that increases acetylcholine levels in the nervous system by inhibiting the acetylcholine esterase enzyme and is especially important in the treatment of neurodegenerative diseases such as Alzheimer's. Extracts obtained from plants are a subject of research in traditional medicine and modern pharmacology due to their effects supporting cognitive functions[31,32]. In our study, the potential of optimized extracts obtained from the fruit of *P. armeniaca* in suppressing cholinesterase enzymes was determined. IC50 values of the obtained findings are shown in Table 3.

Parameters	DPPH (mg Trolox Equi/g)	FRAP (mg Trolox Equi/g)	OSI (TOS/(TAS*10))	TOS (µmol/L)	TAS (mmol/L)	TPC (mg GA Equi/g)	TFC (mg QE Equi/g)
RSM extract	188.89 ± 2.02^{a}	267.03 ± 1.66^{a}	0.065 ± 0.001^{b}	6.242 ± 0.034^{b}	9.560 ± 0.022^{a}	662.480 ± 1.931^{a}	361.660 ± 1.168^{a}
ANN-GA extract	208.72 ± 1.42^{b}	294.88 ± 2.15^{b}	0.052 ± 0.001^{a}	5.176 ± 0.032^{a}	10.042 ± 0.035^{b}	705.967 ± 2.350^{b}	386.173 ± 2.134^{b}

Table 2. Antioxidant parameters of *Prunus armeniaca*. [a]Means having the different superscript letter(s) in the same column are significantly different ($p < 0.05$) according to independent *t* test. DPPH: 2,2-diphenyl-1-picrylhydrazyl radical scavenging activity; FRAP: Ferric reducing antioxidant power; OSI: Oxidative stress index; TOS: Total oxidant status; TAS: Total antioxidant status; TPC: Total phenolic content; TFC: Total flavonoid content

Sample	AChE µg/mL	BChE µg/mL
RSM extract	31.617 ± 1.023^{c}	56.967 ± 0.719^{c}
ANN-GA extract	26.633 ± 0.816^{b}	47.760 ± 1.396^{b}
Galantamine	5.320 ± 0.121^{a}	15.903 ± 0.286^{a}

Table 3. Anticholinesterase activity of *Prunus Armeniaca* fruit. [a]Means with different superscript letters in the same column differ significantly ($p < 0.05$) per Duncan's Test (ANOVA).

Phenolic compounds	LOD (µg/mL)	LOQ (µg/mL)	RSM extract (mg/kg)	ANN-GA extract (mg/kg)
Kaempferol	3.15	10.50	353.12 ± 1.18^{a}	630.06 ± 0.89^{b}
Fumaric acid	7.22	24.08	1287.67 ± 1.53^{a}	2191.62 ± 1.15^{b}
Gallic acid	2.17	7.24	8971.68 ± 0.92^{a}	10658.74 ± 2.05^{b}
Protocatechuic acid	2.21	7.37	4267.95 ± 1.95^{a}	4434.20 ± 0.86^{b}
Caffeic acid	2.19	7.29	19659.93 ± 1.10^{a}	23262.67 ± 1.88^{b}
Naringenin	1.66	5.54	2593.17 ± 0.81^{a}	4165.76 ± 1.06^{b}
Quercetin	4.18	13.93	4777.57 ± 1.96^{a}	5058.23 ± 1.46^{b}
Catechinhyrate	5.47	18.22	1640.90 ± 1.00^{a}	1774.09 ± 1.47^{b}
Vanillic acid	24.74	82.46	623.54 ± 0.89^{a}	1145.02 ± 1.72^{b}
Resveratrol	10.38	34.59	193.21 ± 1.05^{b}	60.54 ± 0.74^{a}
Salicylic acid	0.56	1.88	1255.49 ± 2.11^{b}	765.55 ± 1.61^{a}
2-hydoxycinamic acid	1.37	4.56	974.71 ± 0.55^{b}	900.35 ± 0.97^{a}

Table 4. Phenolic contents of *Prunus Armeniaca* fruit. [a]Means having the different superscript letter(s) in the same line are significantly different ($p < 0.05$) according to independent *t* test. LOD: Limit of Detection; LOQ: Limit of Quantification. Values are expressed in µg/mL as obtained from LC-MS/MS analysis

In our study, we show the AChE and BChE inhibitory effects of extracts obtained from *P. armeniaca* fruit with different extraction methods via IC_{50} values. IC_{50} value expresses the concentration of a substance required to inhibit a specific biological target by 50%, and lower IC_{50} values indicate stronger inhibitory effect[33]. Galantamine used in the study had the lowest IC_{50} values as a comparison group and showed the strongest inhibitory effect on AChE and BChE enzymes (AChE: 5.320 µg/mL, BChE: 15.903 µg/mL). When the extracts obtained by RSM and ANN-GA extraction methods were compared, ANN-GA extract (AChE: 26.633 µg/mL, BChE: 47.760 µg/mL) had lower IC_{50} values compared to RSM extract (AChE: 31.617 µg/mL, BChE: 56.967 µg/mL) and therefore showed stronger inhibitory effect. However, IC_{50} values of both extracts on BChE were higher than IC_{50} values on AChE, suggesting that these extracts showed stronger inhibitory activity against AChE enzyme. It has been reported in the literature that the anticholinesterase activities of extracts obtained from different parts of *P. armeniaca* plant showed variability. It has been reported that the IC_{50} value of AChE activity of the essential oil obtained from *P. armeniaca* leaves is in the range of 97.60–98.50 µg/mL and the IC_{50} value of BChE activity is in the range of 138.30–226.90 µg/mL[34]. These values are considerably higher than the IC_{50} values obtained in our study, which shows that the inhibitory effect of the essential oil obtained from the leaves on AChE and BChE is weaker. Similarly, in another study, it was reported that different extracts of *P. armeniaca* fruit had IC_{50} values of 134.93->500 µg/mL for AChE inhibition and > 500 µg/mL for BChE inhibition[35]. The IC_{50} values obtained in this study indicate that the *P. armeniaca* fruit extracts exhibit a moderate but meaningful inhibitory effect on both AChE and BChE enzymes. Notably, the ANN-GA-derived extract demonstrated stronger inhibition compared to the RSM-derived one, and its IC_{50} values were considerably lower than those reported in previous studies involving apricot or other members of the Rosaceae family. This enhancement may be attributed to the higher phenolic and flavonoid content of the ANN-GA extract, particularly compounds such as kaempferol and gallic acid, which are known to possess cholinesterase inhibitory properties. These findings underscore the critical impact of extraction methods, plant parts, and enzyme sources on anticholinesterase activity. Although the extracts were less potent than the standard drug galantamine, their combined antioxidant and cholinesterase-inhibitory effects highlight the potential of *P. armeniaca* as a promising multi-target candidate for age-related neurodegenerative disorders. Nonetheless, further studies are needed to assess its bioavailability, pharmacokinetics, and safety profile to support its clinical applicability.

Phenolic contents

Plants synthesize various phenolic compounds as part of their defense mechanisms, and these compounds stand out with their antioxidant, anti-inflammatory, and antimicrobial properties[36]. Different phenolic groups such as flavonoids, phenolic acids, tannins, and lignans play an important role in the metabolism of plants and show biological activity in terms of human health[37]. In our study, the phenolic contents of the optimized extract obtained from the fruit part of *P. armeniaca* were scanned on the LC-MS/MS device. The findings are shown in Table 4.

In our study, the amounts of phenolic compounds obtained from *P. armeniaca* fruit vary depending on the extraction method used. In the study, the phenolic contents of the extracts obtained by RSM and ANN-GA methods were compared. The findings obtained show that ANN-GA method generally provides higher phenolic compound yield. Especially, compounds such as kaempferol, fumaric acid, gallic acid, caffeic acid and naringenin were obtained in higher concentrations by ANN-GA method, suggesting that this method may be more effective in the extraction of phenolic compounds. For example, while the amount of caffeic acid reached 23262.67 mg/kg by ANN-GA method, this value was determined as 19659.93 mg/kg by RSM method. Similarly, kaempferol content was almost doubled by ANN-GA. However, it is seen that ANN-GA method has disadvantages for some phenolic compounds. In particular, compounds such as resveratrol and salicylic acid were extracted at higher rates with the RSM method. Resveratrol is a stilbene derivative with low solubility[38], and the extraction conditions of the ANN-GA method may not be suitable for the efficient separation of this compound. Similarly, the amount of salicylic acid was obtained at a lower level with the ANN-GA method compared to the RSM method. This reveals that both methods may have varying effects on different compound types and that the extraction method should be carefully selected depending on the targeted compound. The extraction efficiency of phenolic compounds depends on the optimization ability of the method used[6]. The ANN-GA method can provide higher yields of phenolic compounds by modeling the complex relationships between variables. The ANN-GA method is superior, especially in terms of flavonoid compounds. In contrast, the RSM method may be more effective for certain phenolic acids and stilbene derivatives. Considering the advantages of both methods, it may be beneficial to develop hybrid methods to increase the extraction of certain phenolic compounds. Future studies should focus on optimizing the extraction parameters and evaluating the bioavailability levels of phenolic compounds. In addition, more efficient and sustainable extraction methods can be developed by investigating the effects of factors such as different solvent systems and temperature variables on extraction efficiency. One limitation of the current study is the lack of validation data regarding recovery and intra-/inter-day precision of the LC-MS/MS method. Although LOD and LOQ values were calculated and calibration linearity was confirmed, future studies should include full validation parameters to strengthen analytical robustness.

Conclusion

This study optimized the extraction conditions in order to increase the biological activity potential of extracts obtained from *P. armeniaca* (apricot) fruit. As a result of the analyses, it was determined that the antioxidant capacity, phenolic compound content and biological activity of the extracts optimized with the ANN-GA method were higher than those optimized with the RSM method. Especially when the antiproliferative and anticholinesterase activities were evaluated, it was seen that the extracts obtained with the ANN-GA method were more effective in suppressing the proliferation of cancer cells and inhibiting cholinesterase enzymes. These findings reveal that ANN-GA based optimization is a powerful strategy to increase the extraction efficiency of bioactive compounds. In future studies, the biological mechanisms by which Prunus armeniaca extracts are effective should be investigated in more detail and the molecular pathways that these extracts affect at the cellular level should be investigated. In addition, in vivo toxicity and bioavailability studies should be conducted to determine the safe usage doses of these extracts and their effects on human health should be evaluated more comprehensively. In addition, more data should be obtained in terms of pharmaceutical use by detailing the absorption, distribution and metabolism processes of the extracts with pharmacokinetic analyses. The biological activity can be further increased by combining alternative extraction techniques with the ANN-GA method. Finally, its potential for use in functional food and pharmaceutical sectors should be investigated by evaluating its applicability on an industrial scale. Further studies to be conducted in this direction will contribute to the more effective and safe evaluation of *P. armeniaca* extracts in the field of health.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Author contributions

Conceptualization, M.S, A.G., I.U., E.S., O.K., N.Ç.; methodology, M.S, A.G., I.U., E.S., O.K., N.Ç.; validation, M.S, A.G., I.U., E.S., O.K., N.Ç.; investigation, M.S, A.G., I.U., E.S., O.K., N.Ç.; resources, M.S, A.G., I.U., E.S., O.K., N.Ç.; data curation, M.S, A.G., I.U., E.S., O.K., N.Ç.; writing—original draft preparation, M.S, A.G., I.U., E.S., O.K., N.Ç.; writing-review and editing, M.S, A.G., I.U., E.S., O.K., N.Ç. All authors have read and agreed to the published version of the manuscript.

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Declarations

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Consent to participate

Not applicable.

Additional information

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