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Comparative evaluation of bioactive properties of *Philadelphus coronarius* leaf and flower extracts: Antioxidant and enzyme inhibitory activities

Tuba Eda Arpa Zemzemoğlu[1], Nesibe Arslan Burnaz[1]*

[1] Gümüşhane University, Faculty of Health Sciences, Department of Nutrition and Dietetics, 29100 Gümüşhane, Türkiye

Abstract

This study comparatively evaluated the bioactive properties of *Philadelphus coronarius* leaf and flower extracts, focusing on phenolic composition, antioxidant capacity, and enzyme inhibitory activities. Plant materials were collected, dried, powdered, and extracted using 80% ethanol via ultrasound-assisted extraction. Total phenolic content (TPC), total flavonoid content (TFC), and antioxidant activities (ABTS, DPPH, and FRAP assays) were determined, along with α-glucosidase and acetylcholinesterase inhibitory activities. The leaf extract exhibited significantly higher phenolic and flavonoid contents (4082.81 mg GAE/100 g DW and 3444.17 mg CE/100 g DW, respectively) compared to the flower extract (1864.06 mg GAE/100 g DW and 869.17 mg CE/100 g DW). Similarly, the antioxidant capacities (DPPH, ABTS, and FRAP values) of the leaf extract were found to be significantly higher than those of the flower extract. In enzyme inhibition studies, the leaf extract demonstrated stronger α-glucosidase inhibitory activity (IC_{50}: 0.0211 mg/mL) than the flower extract (IC_{50}: 0.0523 mg/mL). In contrast, acetylcholinesterase inhibition was similar for both extracts. Overall, the findings indicate that *P. coronarius* leaves possess a strong bioactive potential, particularly in terms of phenolic compounds, antioxidant capacity, and α-glucosidase inhibitory activity. Therefore, the leaf part of this species may be considered a promising natural source of antioxidants and functional bioactive compounds.

Keywords: *Philadelphus coronarius*; phenolic; antioxidant activity; α-glucosidase inhibition; acetylcholinesterase inhibition

1. Introduction

Plants are recognized as valuable sources of bioactive compounds and secondary metabolites, serving as the basis for numerous commercial drugs as well as traditional herbal remedies. Medicinal plants are notable for their chemical constituents, which exhibit a wide range of biological activities that may contribute to human health through pharmaceutical and food applications. Moreover, these natural compounds possess considerable economic value for the fragrance, agrochemical, and cosmetic industries [1,2]. Owing to their diverse therapeutic properties, plant-derived bioactive compounds have attracted increasing scientific and industrial interest in recent years [3,4].

Philadelphus coronarius (*P. coronarius*), a member of the family Hydrangeaceae within the order Cornales, is one of the plant species with promising but still insufficiently explored biological potential [5]. Several members of the Hydrangeaceae family have been reported to exhibit antimicrobial, anti-inflammatory, hepatoprotective, and antidiabetic activities [6–9]. However, compared with other representatives of this family, *P. coronarius* has received relatively limited scientific attention, and available data regarding its chemical composition and pharmacological properties remain scarce. Nevertheless, the species has been widely used in traditional medicine for the treatment of various ailments. Previous phytochemical investigations have revealed the presence of flavonoids, triterpenes, coumarins, and phenolic acids in *P. coronarius*, suggesting that this plant may represent a noteworthy source of biologically active constituents [10].

Commonly known as sweet mock orange, *P. coronarius* L. has been cultivated worldwide as an ornamental shrub in parks, landscapes, and home gardens since the sixteenth century. Owing to the pleasant fragrance of its flowers, which resembles that of *Jasminum officinale* L., the plant is widely referred to as "false jasmine" in folk usage. Although the genus

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***Corresponding author:** Nesibe Arslan Burnaz
e-mail: nesibeburnaz@gumushane.edu.tr

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Philadelphus L. comprises a considerable diversity of species, only a limited number are widely cultivated because of their ecological plasticity, adaptability to different environmental conditions, and ornamental value. Among these, *P. coronarius*, *P. microphyllus*, *P. schrenkii*, and *P. caucasicus* are the most prominent taxa [11]. From a biogeographical perspective, *P. coronarius* is native to the North Caucasus, Transcaucasia, and Türkiye and has subsequently been introduced into various parts of Europe, Asia, and North America. Although it is often compared with *J. officinale* because of their similar floral scent, the two species belong to different botanical families and differ considerably in their taxonomic and phytochemical characteristics. The ornamental value, traditional use, and phytochemical profile of *P. coronarius* collectively highlight its potential as a natural source of bioactive compounds. However, comprehensive studies investigating its biological properties remain limited [10,11].

Therefore, the present study aimed to comparatively evaluate the bioactive potential of leaf and flower extracts of *P. coronarius* by determining their total phenolic content, total flavonoid content, antioxidant activity, α-glucosidase inhibitory activity, and acetylcholinesterase inhibitory activity.

2. Materials and methods

2.1. Chemicals and reagents

All chemicals, solvents, and reagents were procured from Merck (Darmstadt, Germany) or Sigma-Aldrich (St. Louis, USA).

2.2. Plant materials and extraction

The *P. coronarius* flowers and leaves used in this study were collected from two different trees on the Gümüşhane University campus in late April 2025. (Fig. 1). The coordinates of the location of *Philadelphus coronarius* are 40◦26′ 14.8″ N 39◦31′ 00.8″ E. The plant material was identified and authenticated by Prof. Dr. Nevzat Batan, and a voucher specimen (*P. coronarius* L., KTUB 1593) has been deposited in the KTUB Herbarium.

After the flowers and leaves of the harvested plant were separated from the stems, they were spread out on filter paper and left to stand in a laboratory setting for 4 days. Then they were left to dry in an oven at 40°C for 2 days. The dried samples were ground into a powder using a metal blender. For extraction, 1 g was weighed from each portion, and 10 mL of solvent (80% ethanol) was added. The samples were extracted in an ultrasonic bath at 30°C for 20 minutes. Afterwards, the sample was placed in a centrifuge and centrifuged at 5°C for 10 minutes at 5000 rpm to clarify the solution. The final volume of the extracts was adjusted to 10 mL [12]. The resulting samples were stored at -18°C for analysis.

Figure 1. Flowers and leaves of *Philadelphus coronarius*

2.3. Total phenolic content determination

The total phenolic content of the samples was determined by the Folin–Ciocalteu method. The method developed by Slinkard and Singleton [13] and previously applied with minor modifications by Ilyasoğlu and Zemzemoğlu [14] was used. First, 100 µL of extract was mixed with 500 µL of Folin–Ciocalteu reagent and incubated for 5 minutes. Then, 400 µL of sodium carbonate solution (1 M) was added, and the mixture was kept in the dark for 1 hour. The absorbance of the reaction mixture was measured at 760 nm using a UV-Vis spectrophotometer (Shimadzu UV-1800, Japan). Results were expressed as mg gallic acid equivalent per 100 g of DW (mg GAE/100 g DW).

2.4. Total flavonoid content determination

The total flavonoid content of the samples was determined by a colorimetric (aluminum chloride) method. According to this method, 250 µL of extract was diluted with 1.25 mL of pure water and then mixed with 75 µL of sodium nitrite solution (5%). After waiting 6 minutes in the dark, 150 µL of aluminum chloride solution (10%) was added, and the mixture was allowed to stand for another 5 minutes. Finally, 1M NaOH and 275 µL of pure water were added and mixed using a vortex mixer. Subsequently, the absorbance of the reaction mixture was measured at 510 nm using a spectrophotometer [15]. Results were expressed as mg catechin equivalent per 100 g of DW (mg CE/100 g DW).

2.5. Antioxidant activity assays

2.5.1. ABTS $^{\bullet+}$ radical scavenging assay

The method developed by Re et al. [16] and applied with minor modifications by Arslan Burnaz and Aktürk [17] was used in this study. A stable 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS$^{\bullet+}$) radical

cation solution was prepared one day in advance by mixing 7 mM ABTS radical solution and 2.45 mM potassium persulfate solution in pure water. The solution was left in the dark for 16 hours. The following day, the solution absorbance was adjusted to 0.70 (±0.02) units at 734 nm. For the analysis, 50 µL of the extract was mixed with 1.95 mL of the $ABTS^{\bullet+}$ solution. The mixture was left to stand in the dark for 20 minutes. Subsequently, the absorbances of the reaction mixtures were measured at 734 nm using a spectrophotometer. Trolox was used as a standard antioxidant (positive control), and the results were expressed as mmol Trolox equivalent per 100 g of DW (mmol TE/100 g DW).

2.5.2. DPPH• radical scavenging assay

The method developed by Brand-Williams et al. [18] and previously applied with minor modifications by Ilyasoğlu and Burnaz [19] was used. 50 µL of extract was mixed with 1.45 mL of 2,2-diphenyl-1-picrylhydrazyl radical (60 µM DPPH•) solution. After an incubation in the dark for 1 hour, the absorbance of the reaction mixture was measured at 515 nm using a spectrophotometer. Trolox was used as a standard antioxidant (positive control), and the results were expressed as mmol TE/100 g DW.

2.5.3. FRAP (ferric reducing antioxidant power) assay

The FRAP method, developed by Benzie and Strain [20] and previously applied with minor modifications by Burnaz [21], was used. The working FRAP reagent solution was prepared by mixing 10 mM TPTZ (in 40 mM HCl), 20 mM iron chloride, and 300 mM sodium acetate buffer solutions in a 1:1:10 ratio. Then, 50 µL of sample was added to 1.95 mL of the working FRAP solution, mixed thoroughly, and incubated in the dark for 20 minutes. The absorbance of the reaction mixture was measured at 595 nm using a spectrophotometer. Trolox was used as a standard antioxidant (positive control), and results were expressed as mmol TE/100 g DW.

2.6. Enzyme inhibitory assays

2.6.1. α-Glucosidase inhibition assay of extracts

The α-glucosidase (from *Saccharomyces cerevisiae*) inhibition assay was conducted according to the published method with minor modifications [22]. The α-glucosidase and p-nitrophenyl-D-glycopyranoside (p-NPG) solutions were prepared with phosphate buffer (0.1 M, pH 6.9). First, 730 µL distilled water and 200 µL phosphate buffer were transferred to a quartz cuvette. Then, 20 µL of enzyme and sample solutions were added, respectively. Finally, 50 µL of p-NPG was added and mixed. Enzyme activity absorbance was measured at 405 nm at 0 and 3 minutes. For the control test cuvette, measurements were made by ensuring all pipetting except the sample (100% activity). This analysis was performed on at least 5 different volumes of the sample. Enzyme activity (%) - absorbance graphs were drawn, and inhibition concentration 50% (IC_{50}) values were calculated. As a positive control, acarbose was used in the assay, and its inhibitory effect was measured under the same conditions as the samples.

2.6.2. Acetylcholinesterase inhibition assay of extracts

The cholinesterase inhibition assay was performed by an already established method reported by Ellman et al. with minor modifications [23].

First, a 20 mM Tris-HCl (Trizma; pH 7.5) buffer was prepared to dilute the enzyme. Additionally, 1 M Tris-HCl (Trizma; pH 8.0) buffer, 5,5′-dithiobis-2-nitrobenzoic acid (DTNB, substrate), and acetylthiocholine iodide (substrate) solutions were prepared to be used in the analysis.

For the analysis, the following were added to the quartz cuvette in sequence: 780 µL pure water, 100 µL 1M buffer (pH 8.0), 50 µL DTNB, 20 µL enzyme, and the sample (extract/inhibitor). Finally, 50 µL of acetylthiocholine iodide (substrate) was added, the cuvette was closed, and the cuvette was inverted. Enzyme activity absorbance was measured at 412 nm at 0 and 5 minutes. For the control test cuvette, measurements were made by ensuring all pipetting except the sample (100% activity). This analysis was performed on at least 5 different volumes of the sample. Enzyme activity (%) - absorbance graphs were drawn and inhibition concentration 50% (IC_{50}) values were calculated. As a positive control, galantamine hydrobromide (Galantamine HBr) was used in the assay, and its inhibitory effect was measured under the same conditions as the samples.

2.7. Data analysis

Data were analyzed by using one-way analysis of variance (ANOVA) followed by Duncan's multiple range test for enzyme inhibitory activity assays involving multiple groups, while an independent samples t-test was used for antioxidant activity analyses comparing leaf and flower extracts. SPSS version 25.0 statistical software was used for these analyses. All assays were performed in triplicate, and the results were expressed as the mean ± standard deviation (SD). Statistical significance was defined as $p < 0.05$.

3. Results and discussion

Total phenolic content (TPC), total flavonoid content (TFC), and antioxidant capacities (DPPH, ABTS, and FRAP) of different parts (flower and leaf) of the *P. coronarius* plant are presented in Table 1. The results

demonstrated that different parts of *P. coronarius* differed significantly in their bioactive compound content and antioxidant capacity. Among the tested plant parts, the leaf extract exhibited consistently higher values than the flower extract for all evaluated parameters. The total phenolic content of the leaf extract was determined to be 4082.81 mg GAE/100 g DW, whereas the corresponding value for the flower extract was 1864.06 mg GAE/100 g DW. Similarly, the total flavonoid content was markedly higher in the leaf extract (3444.17 mg CE/100 g DW) than in the flower extract (869.17 mg CE/100 g DW). These findings indicate that the leaf extract constitutes a richer source of phenolic and flavonoid compounds compared with the flower extract. The antioxidant activity results were also consistent with the phenolic and flavonoid contents. The DPPH radical scavenging activity of the leaf extract was determined as 332.72 mmol TE/100 g DW, which was significantly higher than the value measured for the flower extract (90.72 mmol TE/100 g DW) ($p < 0.05$). Likewise, the ABTS radical scavenging capacity was 28.71 mmol TE/100 g DW in the leaf extract and 7.00 mmol TE/100 g DW in the flower extract. Examination of the FRAP results also showed that the leaf extract had a higher reducing power, with a value of 18.14 mmol TE/100 g DW, compared to the flower extract (5.02 mmol TE/100 g DW). The differences among the means indicated by different letters in the table were found to be statistically significant ($p < 0.05$).

Overall, the *P. coronarius* leaf extract was shown to be superior to the flower extract in terms of both total phenolic and flavonoid compound contents as well as antioxidant activity values. This suggests that the leaf part of the plant may serve as a more potent natural source of antioxidant compounds. Petó et al. (2022) investigated the antioxidant capacity of the leaf and flower parts of *P. coronarius* and reported that the DPPH radical scavenging inhibition of the flower extract (92.24 ± 10.09%) was numerically higher than that of the leaf extract (86.63 ± 6.49%), although this difference was not statistically significant [6]. In contrast, the ABTS (40.54 ± 9.77 mmol TE/g DW), FRAP (164.62 ± 52.75 μmol TE/g), and CUPRAC (423.35 ± 71.07 μmol TE/mL) values were found to be significantly higher in the flower extract than in the leaf extract. For the leaf samples, these values were determined as 18.37 ± 4.73 mmol TE/g DW, 77.97 ± 46.01 μmol TE/g, and 222.42 ± 21.04 μmol TE/mL, respectively. In the same study, total polyphenol and flavonoid contents were also evaluated; the total polyphenol content was 59.31 ± 4.36 mg GAE/100 g in the leaves and 54.83 ± 9.74 mg GAE/100 g in the flowers. Likewise, the flavonoid content was reported as 1.97 ± 1.49 mg QE/100 g in the leaves and 1.91 ± 0.82 mg QE/100 g in the flowers, and no statistically significant difference was observed between the leaf and flower samples for either parameter. The differences observed between the present study and the findings reported by Petó et al. [6] are likely attributable to multiple interacting factors rather than a single cause. Although lyophilization may contribute to improved preservation of phenolic compounds and thus influence measured antioxidant activity, methodological differences such as extraction solvent type, solvent polarity, extraction conditions (time, temperature, and solid–liquid ratio), and analytical variability between assays are also expected to play a significant role. In addition, environmental and biological factors, including geographical origin, soil composition, climatic conditions, and the developmental stage of the plant material at harvest, can substantially affect the biosynthesis and accumulation of secondary metabolites. Furthermore, differences in organ-specific metabolite distribution and stress-related metabolic responses may explain the higher antioxidant activity observed in leaves in the present study compared to the higher activity reported in flowers by Petó et al. (2022). Taken together, these findings suggest that antioxidant capacity in P. coronarius is highly dependent on both intrinsic biological factors and extrinsic experimental conditions.

Sharopov et al. (2020) reported that the antioxidant capacity of *P.* × *purpureomaculatus* varied markedly depending on both the plant part and the extraction method [24]. In their study, methanolic stem extracts exhibited the strongest radical-scavenging activity, showing lower DPPH IC_{50} (89.4 ± 1.2 μg/mL) and ABTS IC_{50} (50.1 ± 0.6 μg/mL) values than methanolic leaf extracts (125.3 ± 1.0 and 111.6 ± 2.4 μg/mL, respectively) and the essential oil obtained from leaves (4830.1 ± 5.5 and 3218.7 ± 4.0 μg/mL, respectively). A similar trend was observed in the FRAP assay, where methanolic stem and leaf extracts showed considerably higher reducing power (236.4 ± 0.5 and 227.1 ± 1.4 mM $FeSO_4$/mg extract, respectively) than the leaf essential oil (74.8 ± 0.8 mM $FeSO_4$/mg extract) [24].

Table 1. Total phenolic/flavonoid contents and antioxidant capacities of different parts of P. coronarius

Plant Parts	TPC mg GAE /100g DW	TFC mg CE/100g DW	DPPH mmol TE/100g DW	ABTS mmol TE/100g DW	FRAP mmol TE/100g DW
Flower	1864.06±11.05	869.17±7.22	90.72±0.91	7.00±0.08	5.02±0.09
Leaf	4082.81*±11.05	3444.17*±26.02	332.72*±8.06	28.71*±0.58	18.14*±0.33

* indicates significant difference at $p < 0.05$. Statistical analysis was carried out between the leaf and the flower by performing a t-test. ± standard deviation.

Table 2. IC_{50} values of the ethanolic *P. coronarius* extracts for the analyzed enzymes*

Samples/Standards	Inhibition of α-glucosidase* IC_{50} (mg/mL)	Inhibition of acetylcholinesterase* IC_{50} (mg/mL)
P. coronarius flower extract	0.0523^{a}±0.0019	0.1286^{a}±0.0029
P. coronarius leaf extract	0.0211^{b}±0.0003	0.1345^{a}±0.0068
Acarbose	0.0081^{c}±0.0002	ns
Galantamine HBr	ns	0.0012^{b}±0.00003

The assays were done in triplicate, and results were expressed as mean ± standard deviation (n=3). Means within the same column followed by different superscript letters are significantly different ($p < 0.05$) according to post-hoc Duncan's multiple range test. ns: not studied.

These findings indicate that antioxidant performance is strongly influenced by both the extraction solvent and the plant matrix and suggest that polar methanolic extracts contain compounds with greater radical-scavenging and reducing potential than the corresponding essential oil fraction.

In a study conducted by Ivković et al., the anti-aging potential of 17 different flower petal extracts was evaluated using a multidisciplinary bioanalytical approach. Within this context, petals of Philadelphus pubescens were also included. The results indicated that the DPPH radical scavenging activity of this plant was 105±8 μmol TE/g, while the ABTS activity was 88±3 μmol TE/g. In addition, the total phenolic content was reported as 20±1 mg GAE/g, and the total flavonoid content as 52 mg rutin equivalents/g [25].

Similarly, in a study carried out by Maslennikov et al., the polyphenol content and water-soluble antioxidant capacity of several shrub species grown in different functional zones of Kaliningrad were investigated. According to their findings, the total phenolic content of Philadelphus coronarius ranged between 22.41±2.19 and 23.45±2.28 mg/g, while the water-soluble antioxidant content ranged from 6.82±0.64 to 7.54±0.72 mg/g [26].

The IC_{50} values obtained from α-glucosidase and acetylcholinesterase inhibition assays of the ethanolic extracts of *P. coronarius* are presented in Table 2. These results provide a comparative overview of the inhibitory potential of the different plant parts against the analyzed enzymes.

According to the one-way ANOVA followed by Duncan's multiple range test, all samples showed statistically significant differences in α-glucosidase inhibitory activity ($p < 0.05$). Acarbose exhibited the lowest IC_{50} value (0.0081 mg/mL), indicating the strongest inhibitory activity, followed by the leaf extract (0.0211 mg/mL) and the flower extract (0.0523 mg/mL). The results demonstrate that the leaf extract possesses significantly higher inhibitory potential than the flower extract, although both were less active than the standard drug. Since lower IC_{50} values correspond to higher enzyme inhibition, the observed activity ranking was acarbose > leaf > flower. This suggests that the bioactive constituents responsible for α-glucosidase inhibition are more concentrated or more effective in the leaf matrix compared to the flower.

The coefficients of determination (R^2) ranged from 0.9916 to 0.9974. Enzyme activity (%) graphs of samples and positive control acarbose are shown in Fig. 2. The inclusion of acarbose allows direct comparison of samples' inhibitory effects against a standard α-glucosidase inhibitor.

The acetylcholinesterase inhibitory activities of the samples are also summarized in Table 2. The IC_{50} value for galantamine HBr, used as a positive control, was determined to be 0.0012 mg/mL. This low value indicates that galantamine HBr is a potential acetylcholinesterase inhibitor and confirms the accuracy of the method. Statistical analysis revealed that galantamine HBr showed a significantly lower IC_{50} value compared to the plant extracts ($p < 0.05$), confirming its strong inhibitory potency as a standard compound. In contrast, the IC_{50} values of the flower (0.1286 mg/mL) and leaf (0.1345 mg/mL) extracts were statistically similar ($p > 0.05$), as indicated by the same grouping letter. These findings indicate that both extracts exhibit

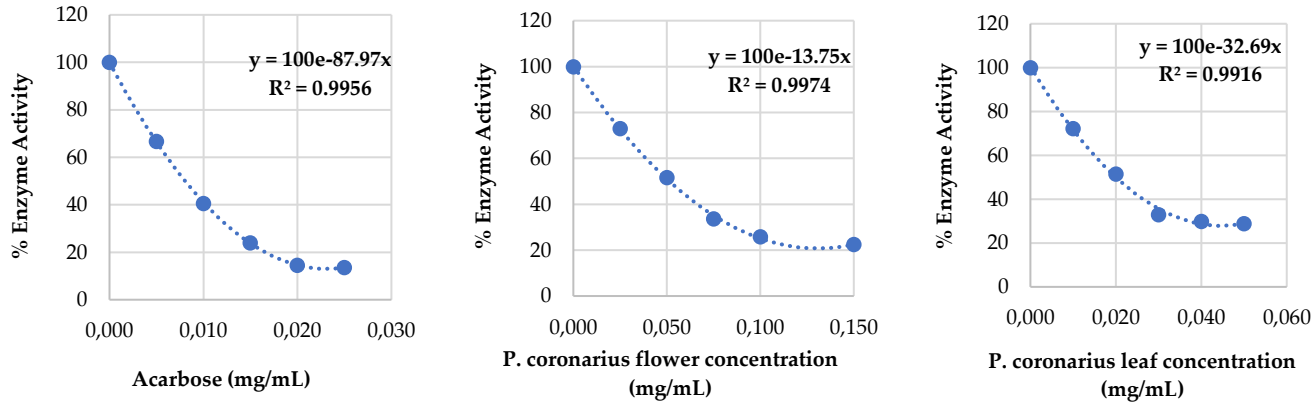

Figure 2. Dose–response curves of α-glucosidase inhibition by acarbose and *P. coronarius* flower and leaf extracts

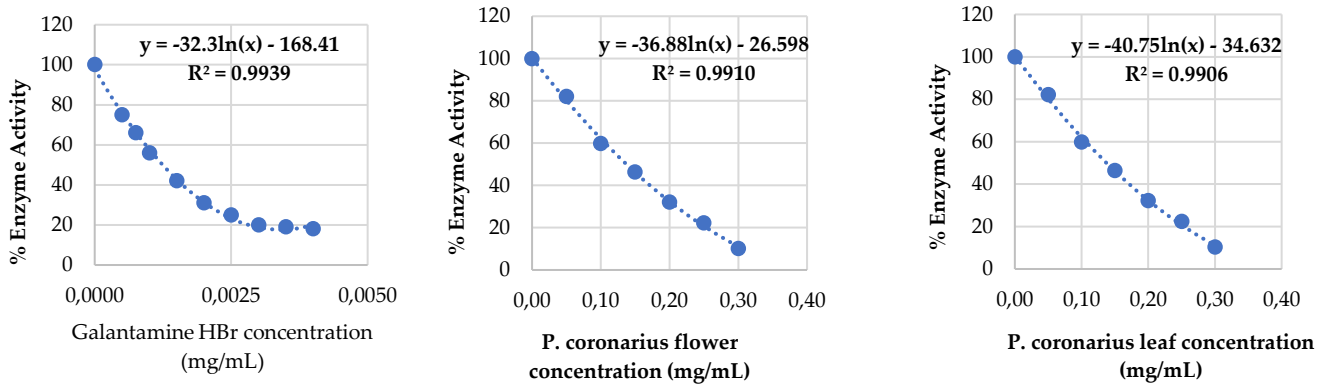

Figure 3. Dose–response curves of acetylcholinesterase inhibition by galantamine HBr and *P. coronarius* flower and leaf extracts

moderate and comparable acetylcholinesterase inhibitory activity, but their effectiveness is considerably lower than that of galantamine. The lack of significant difference between the plant parts suggests a similar distribution of bioactive compounds responsible for acetylcholinesterase inhibition.

The coefficients of determination (R^2) ranged from 0.9906 to 0.9939. Enzyme activity (%) graphs of samples and positive control galantamine HBr are shown in Fig. 3. The inclusion of galantamine HBr allows direct comparison of samples' inhibitory effects against a standard acetylcholinesterase inhibitor.

In contrast to the limited number of studies focusing mainly on the phytochemical composition and antioxidant properties of *P.coronarius*, the present study provides a more comprehensive biological evaluation by investigating both α-glucosidase and acetylcholinesterase inhibitory activities. To the best of our knowledge, this is among the first reports addressing enzyme-targeted bioactivity in this species, thereby extending its potential relevance beyond antioxidant capacity to include antidiabetic and neuroprotective perspectives.

4. Conclusion

In conclusion, the present study demonstrated that the bioactive potential of *Philadelphus coronarius* varied markedly depending on the plant part analyzed. Among the tested samples, the leaf extract exhibited significantly higher total phenolic content, total flavonoid content, and antioxidant activity than the flower extract, indicating that the leaves constitute a richer source of antioxidant phytochemicals. The consistently higher DPPH, ABTS, and FRAP values observed in the leaf extract further support its stronger radical-scavenging and reducing capacity. In addition, the leaf extract showed greater α-glucosidase inhibitory activity than the flower extract, suggesting a more pronounced potential for modulating carbohydrate-hydrolyzing enzymes.

This study extends the current knowledge on *P. coronarius* by demonstrating its potential α-glucosidase and acetylcholinesterase inhibitory activities, suggesting possible antidiabetic and neuroprotective relevance beyond its previously reported antioxidant properties.

In contrast, both plant parts exhibited comparable acetylcholinesterase inhibitory activity, indicating a similar distribution of compounds responsible for this effect. Overall, these findings suggest that *P. coronarius*, particularly its leaves, may serve as a promising natural source of bioactive compounds with antioxidant and enzyme inhibitory properties. The results also highlight the importance of plant part selection when evaluating the functional and pharmacological potential of medicinal and ornamental species. Since the observed activities may be influenced by extraction conditions and the qualitative composition of phytochemicals, further studies focusing on the isolation and characterization of individual bioactive constituents are warranted. Such investigations would contribute to a better understanding of the mechanisms underlying the biological activities of *P. coronarius* and support its possible utilization in pharmaceutical, nutraceutical, and functional food applications.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Nesibe Arslan Burnaz: Conceptualization, methodology, investigation, formal analysis, data curation, writing – original draft preparation, visualization, supervision, and approval of the final manuscript.

Tuba Eda Arpa Zemzemoğlu: Conceptualization, methodology, investigation, writing – original draft preparation, writing – review and editing, and approval of the final manuscript.

Use of Generative AI

The authors declare that generative artificial intelligence (AI) tools were used solely for language editing, grammar improvement, and enhancement of manuscript readability. All scientific content, data analysis, interpretation of results, and conclusions were developed and verified by the authors. The authors take full responsibility for the accuracy and integrity of the manuscript.

Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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