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Determination of The Antimicrobial, Antioxidant and Cytotoxic Activity of *Paulownia tomentosa* Steud.

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ABSTRACT

Paulownia tomentosa, used in traditional Chinese medicine, is used in the treatment of diseases such as bronchitis and asthma thanks to its biological activities. In addition, it is known to have antimicrobial, antioxidant, anticancer effects and it is also used in the treatment of diseases such as dysentery, gonorrhea, hemorrhoids. In this study, the antimicrobial activity of extracts obtained from methanol solvent of flower and petal parts of *P. tomentosa* was determined according to the disk diffusion method. The antioxidant activity of the different concentrations of the extracts obtained from methanol solvent of flower and petal extracts was determined via the 2,2-diphenyl-1-picrilhydrazyl (DPPH) radical scavenging capacity method. Anticancer activity of different concentrations of extracts obtained from solvents such as methanol, ethanol and hexane was determined using the 3- (4,5-dimethylthiazole-2-yl) -2,5-diphenyl tetrazolium bromide (MTT) test method. As a result, it was found that methanol extract of the flower part of *P. tomentosa* showed the best antimicrobial activity against *S. aureus* (18 mm). It was determined that antioxidant activity of *P. tomentosa* increased depend to increasing concentrations. It was concluded that *P. tomentosa* has the best cytotoxic effect in hexane extract.

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Paulownia tomentosa Steud.'un Antimikrobiyal, Antioksidan ve Sitotoksik Etkilerinin Belirlenmesi

ÖZET

Geleneksel Çin tıbbında kullanılan *Paulownia tomentosa* sahip olduğu biyolojik aktiviteler sayesinde bronşit ve astım gibi hastalıkların tedavisinde kullanılmaktadır. Bunun yanı sıra antimikrobiyal, antioksidan, antikanser gibi etkilerinin olduğu ve dizanteri, bel soğukluğu, hemoroid gibi hastalıkların tedavisinde de kullanıldığı bilinmektedir. Bu çalışmada *P. tomentosa*'nın çiçek, petal, kabuk, yaprak ve odun kısımlarının metanol çözücüsünden elde edilen ekstraklarının antimikrobiyal aktivitesi disk difüzyon metoduna göre belirlenmiştir. Çiçek ve petal kısımlarının metanolden elde edilen ekstraktının farklı konsantrasyonlarının antioksidan aktivitesi 2,2-difenil-1-pikrilhidrazil (DPPH) radikal süpürücü kapasitesi yöntemine göre tespit edilmiştir. Metanol, etanol ve hekzan gibi çözücülerden elde edilen ekstraktlarının farklı konsantrasyonlarının antikanser aktivitesi 3- (4,5-dimetiltiyazol-2-iil) -2,5-difenil tetrazolium bromür (MTT) test yöntemi kullanılarak belirlenmiştir. Sonuçta en iyi antimikrobiyal aktiviteyi *P. tomentosa*'nın çiçek kısmının metanol özütü *S. aureus*'a (18 mm) karşı gösterdiği tespit edilmiştir. *P. tomentosa*'nın antioksidan aktivitesinin artan konsantrasyonlara bağlı olarak arttığı belirlenmiştir. *P. tomentosa*'nın en iyi sitotoksik etkiyi hekzan ekstresinde gösterdiği tespit edilmiştir.

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INTRODUCTION

Since ancient times, societies have benefited primarily from plants to obtain nutrients and treat diseases. It has come to date day with some changes and developments in usage patterns (Adıgüzel and Kızılaslan, 2016). Especially with the increasing number of chronic diseases, the importance of the drug used in treatment, the amount of the drug and the desired physiological response have increased the use of herbal medicine in the World (Doğan & Avcı, 2018). These herbal medicines used are known to be effective in the treatment of cancer prevention, joint pain, treatment of anxiety and depression, back pain, heart disease and kidney diseases (Eisenberg et al., 1998; King and Pettigrew, 2003; Faydaoğlu and Sürücüoğlu, 2011; Kardaş, 2019). For this purpose, studies and evaluation of the biological activities of plant extracts are needed.

The *Paulownia tomentosa* Steud., called the princess tree, belongs to the Scrophulariaceae family, is tree a fast growing and deciduous has economic value (San Jose Mdel et al., 2014). The bark, timber and flowers of the paulownia tree are used in the treatment of infectious and inflammatory diseases in traditional Chinese medicine (Ji et al., 2015). It is also known to be used in the treatment of diseases such as hemorrhoids, traumatic bleeding, bacteriological diarrhea, hypertension, dysentery and as an expectorant in upper respiratory diseases (Uğuz, 2018; Lee et al., 2018).

In this study, It was aimed to determine the antimicrobial activity of the extracts of *P. tomentosa* obtained from methanol solvent of its flower and petals, and to determine antioxidant activity of different concentrations of flower and petal extracts obtained from methanol and to determine anticancer activity of different concentrations of extracts obtained from solvents including methanol, ethanol and hexane.

MATERIAL and METHODS

Collection and Identification of the Material

P. tomentosa was collected from the Elazig-Fırat University campus in 2019. The taxonomic identification of plant material was determined by using the Flora of Turkey (Davis, 1970, 1984, 1985) and with help of systematic-botanic specialist Prof. Dr. Şemsettin Civelek from Fırat University.

Obtaining and Preparing the Material

The flower and petal parts of *P. tomentosa* were dried and grounded and 5 g of each extrac were taken. Extraction performed for 7 hours in a soxhlet device using 150 ml of %96 methanol, ethanol and hexane solvents. Then, the alcohol remaining in the extracts was concentrated at 40ºC using a rotary evaporator.

Test Microorganisms

In this study; *Staphylococcus aureus* ATCC25923, *Escherichia coli* ATCC25322, *Candida albicans* FMC17 and *Trichophyton sp.* microorganisms were used. Microorganism cultures were obtained from Fırat University, Faculty of Science, Department of Biology, Microbiology Laboratory culture collection.

Preparation of Microorganism Cultures and Testing Antimicrobial Effect

Antimicrobial activity of the methanol extracts of flower and petal parts of *P. tomentosa* was determined according to the disk diffusion method (Collins and Lyne, 1987). Bacterial strains (*Staphylococcus aureus* ATCC25923, *Escherichia coli* ATCC25322) were inoculated in Nutrient Buyyon (Difco) and incubated at 35±1°C for 24 hours. Yeast strains (*Candida albicans* FMC17) were inoculated in Malt Extract Buyyon (Difco), dermatophyte fungi (*Trichophyton sp.*) were inoculated in Glucose Sabouroud Buyyon (Difco) and incubated at 25 ± 1°C for 48 hours. The culture of prepared bacteria, yeast and fungi in broth are respectively; was inoculated into Müeller Hinton Agar, Sabouraud Dextrose Agar and Potato Dextrose Agar at a rate of 1% (10^6 bacteria ml, 10^4 yeast ml, 10^4 fungi ml). After shaking thoroughly, 25 ml was poured in sterile petri dishes with a diameter of 9 cm and homogeneously of the medium was dispersed. The discs (6 mm diameter) each of which 100 µl of different extracts were impregnated, and added to the appropriate agar media inoculated with microorganism. Then, petri dishes were stored at 40 °C for 2 h. The inoculated petri dishes were incubated at 37±0.10 °C at 24 h for bacterial strains and also at 25±0.10 °C at 72 h for yeasts and dermatophyta fungi. As a control, different standard discs were used for bacteria (Streptomycin sulfate 10 µg disk) and yeasts (Nystatin 30 µg disk). Dimethyl sulfoxide (DMSO) was used for negative control. Inhibition zones formed on the medium at the end of the period were evaluated in mm.

Testing the Antioxidant Effect

The antioxidant activity of the different concentrations of the methanol extract of the mixture of flower and petal parts (1:1) of *P. tomentosa* was determined according to the 2.2-diphenyl-1-picrilhydrazyl (DPPH) radical scavenging capacity method (Cuendet et al., 1997; Kirby and Scmidt, 1997). The solution was prepared in methanol at a concentration of 2 mg ml of the extract obtained. The prepared solution was diluted four times and the calibration curve of DPPH was obtained. By taking 40 µl of the prepared solution, 160 µl of DPPH solution was added. After thorough mixing, the mouth was closed and kept in the dark for 30 minutes. The same procedures were repeated for all

concentrations and methanol was used as a control. At the end of this period, the absorbances of each mixture were read at 517 nm in the spectrophotometer. % inhibition values were calculated;

$I(\%) = (Acontol - Asample / Acontrol) \times 100$ (1)

Testing The Cytotoxic Effect

Cell culture

Breast cancer cell line used in this study was supplied from İnönü University and Erzurum Technical University and cultured in DEMEM medium supplemented with 2 mM L-Glutamine, 1% Penicillin-Streptomycin and 10% FBS. Cells were incubated at 37°C in a 5% CO_2 incubator. The stock solution was prepared in DMSO.

MTT reduction assay

The anticancer activity of hexane, ethanol and methanol extracts of *P. tomentosa* was determined by using 3-(4,5dimethylthiazol–2-iyl)-2,5-diphenyl tetrazolium bromide (MTT) assay method. MTT, which is one of the tetrazolium salts, is transformed into a structure called formazan by the reduction of the electron and provides the color change. Briefly, the tetrazolium rings that are broken by the active mitochondria causing the color change in the livinge cells (Mossman, 1983).

The MDA-MB-231 cell line, grown in 25 cm^2 flasks, was confluent and the medium was removed by washing with 5 ml sterile PBS solution. Then, 1 ml of Trypsin-EDTA was added to the flask and incubated for 2 minutes at 37°C in 5% CO_2 medium. After the cells were removed from the surface, trypsin-EDTA was inactivated by adding 5 ml medium. Cells were removed from the flask and centrifuged at 1200 rpm for 5 minutes. The supernatant was discarded and the pellet was dissolved in a new medium. Then, the cells were counted and their concentration adjusted to 5000 cells per well. 100 µl was added to 96 well plate wells. Then, it was incubated for 24 hours at 37°C in 5% CO_2 medium. After incubation, 100 µl from different concentrations (1/1000, 1/2000, 1/4000) of methanol, ethanol and hexane extracts of *P. tomentosa* were added and incubated for 24 hours at 37°C in 5% CO_2 medium. At the end of the incubation, 20 µl of MTT solution was added and at the end of 4 hours incubation, absorbance measurements at 570 and 540 nm wavelengths were made. Doxorubicin was used as positive control and DEMEM as negative control.

Statiscial Analyses

The absorbance values measured by ELISA plate reader were compared with the control groups and plotted. Statistical analysis was performed using SPPS 21, Paired Samples T Test was used to determine the differences between the groups. Quantitative data were expressed as mean ± standard deviation (Mean ± SD) and $p < 0.05$ was considered significant level.

RESULTS and DISCUSSION

Antimicrobial Effect

Antimicrobial activity results against *S. aureus*, *E. coli*, *C. albicans* and *Trichophyton sp.* of the methanol extracts of *P. tomentosa*'s flower and petal parts are given in Table 1.

Table 1. Antimicrobial effect of flower and petal parts of *P. tomentosa*
Çizelge. P. tomentosa'nın çiçek ve *petal kısımlarının antimikrobiyal etkisi*

	S. aureus	*E. coli*	*C. albicans*	*Trichophyton sp*
P.T- Flower (*P.T-Çiçek*)	18	16	-	13
P.T- Petal (*P.T-Petal*)	-	12	8	9
Control (*Kontrol*)	12	10	30	11

P.T Flower: Flower part of *P. tomentosa*; P.T Petal: Petal part of *P. tomentosa*

Methanol extracts of flower part of *P. tomentosa* showed antimicrobial effects against *S. aureus* (18mm). But, it was determined that the methanol extract of petal part sustained no antimicrobial effect (Table Çizelge 1).

Inhibition zones of methanol extracts of the flower and petal parts of *P. tomentosa* against *E. coli* were determined to be 16mm and 12mm, respectively (Table 1).

It was determined that methanol extracts of the petal part of *P. tomentosa* had little antimicrobial effect against *C. albicans* (8mm) and the flower part had no antimicrobial effects (Table 1).

Inhibition zones of the methanol extracts of flower and petal parts of *P. tomentosa* against *Trichophyton sp.* were determined as 13mm and 9mm, respectively (Table 1).

In a study, it was determined that some C-granile flavanones selected from *P. tomentosa* fruits have minimum inhibitor concentrations between 2-64 µg ml against MRSA 287, MRSA 4211, MRSA 6975, MRSA 630 and MRSA 62059 strains (Navrátilová et al., 2013). The antiviral effect of methanol extract of flowers of the same species against enterovirus 71 and coxacivirus A16 has been tested and the results have only been reported to show antiviral effects against enterovirus 71 (Ji et al., 2015). Minimum inhibitor concentrations of C6 granulated compounds of *P. tomentosa* (30-O-methyl-50-hydroxydiplacon, 30-O-

methyl-50-O-methyldiplacone, 30-O-methyldiplacol, 30-O-methyldiplacone, mimulo and diplacone) have been found between 2-64 µg ml against MRSA 1903, MRSA 63718, MRSA 3202, MRSA 62097, MRSA 67755 and MRSA 1679 strains (Navrátilová et al., 2016). The antiviral effect against Brunhilde strain poliovirus type 1 and Leon strain type 3 was studied using *P. tomentosa* Hela cells. IC50 values were determined to be 0.3 µg mL and 0.6 µg mL, respectively (Kang et al., 1999). Eight different C-6-geranilflavonoids were isolated from the ethanol extract of the fruits of *P. tomentosa* and their antibacterial effect was tested. According to the results obtained, it shown antibacterial activity against at 2-16 µg mL against *B. cereus*, 4-8 µg mL against *B. subtilis*, 4-8 µg mL against *E. faecalis*, 2-32 µg mL against L. *monocytogenes*, 2-16 µg mL against *S. aureus*, 2-32 µg mL against *S. epidermidis* but it didnt show antibacterial activity against *P. aeruginosa*, *S. enteritidis* and *E. coli* (Smejkal et al., 2008). It was reported in the study that the inhibition zones of *P. elongata* leaves and silage extract against *S. enterica*, *P. aeruginosa*, *S. aureus*, S. pyogenes, *P. alvei* and *C. albicans* ranged between 12.7-17.3 mm (Popova and Baykov, 2013). The extract from the epicarp of the fruits of *P. fortunei* and *P. tomentosa* showed antimicrobial activity against *S. aureus* and *B. subtilis*, while showed lower antimicrobial activity against *S. carlsbergensis* and *E. coli* (Cercos, 1982). In a different study, the antibacterial and antifungal activity of the DMSO extract of the oil obtained from the seed of *Ceplararia syriaca* (L.) was investigated. In the results obtained, it has been determined that it shows different antimicrobial effects (10.66-2.6 mm) at different concentration against *K. pneumoniae*, S. aureus, *P. vulgaris*, *E. coli*, *S. marcescens*, *S. epidermis*, *E. faecium*, *P. aeruginosa*, *B. subtilis*, *S. typhimurium*, *S. enteritidis*, *L. innocua*, *E. faecalis*, *P. fluorescens*, *S. infantis*, *E. aerogenes*, *S. kentucky*, *E. durans*. It created a 2.16 mm inhibition zone against *C. albicans* at a concentration of 70 µl ml (Atalan et al., 2020). While *A. acerosum* created different inhibition zones in different concentrations against *E.coli* and *S.aureus*, it did not show antifungal activity against *C. albicans*. In the same study, it was reported that extracts of *A. microcephalum* at different concentrations did not show antimicrobial effects against *E.coli*, *S.aureus* and *C. albicans* (Bülbül et al., 2018). It has been determined that *Gypsophila laricina*, *Centaurea aphrodisea*, *Centaurea polyclada* and *Limoniopsis davisii* form 3-16.6 mm inhibition zone against *S. aureus* at different concentrations (Tozyılmaz et al., 2020). When the obtained results are compared with the results from previous studies and species such as *Gypsophila laricina*, *Centaurea aphrodisea*, *Centaurea polyclada* and *Limoniopsis davisii*, *A. acerosum*, *A. microcephalum*, *Ceplararia syriaca*, it is seen that their antibacterial and antifungal effects deffered with the particular solvents, microorganisms and plant materials used in the studies.

Antioxidant Effect

The inhibition percentage of the DPPH radical of different concentrations of the methanol extract of the flower and petal parts of *P. tomentosa* in is shown in Table 2.

Table 2. Percentage of inhibition of the DPPH radical of flower and petal parts of *P. tomentosa*
Çizelge 2. P. tomentosa'nın çiçek ve petal kısımlarının DPPH radikalinin inhibisyon yüzdesi

Concentration *Konsantrasyon*	Percentage of inhibition of the DPPH radical *DPPH radikalinin inhibisyon yüzdesi*
2 mg ml	28.195
1 mg ml	23.684
0.5 mg ml	10.902
0.25 mg ml	9.022
0.125 mg ml	1.127

According to the results obtained, DPPH radical scavenging effect of the methanol extract of flower and petal parts of *P. tomentosa* on the was increased depend to increasing concentrations (Table 2).

The IC50 values of the DPPH radical scavenging effect of *P. tomentosa*'s butanol, ethylacetate, chloroform, methanol and hexane extracts were determined to be %0.008, %0.007, %0.0166, %0.0316, and %0.74 mg ml, respectively (Smejkal et al., 2007). The antioxidant effect of some flavanides of the same species was tested using different methods. $TEAC_{ABTS}$ and $TEAC_{DPPH}$ were determined to be in the range of 3.2-0.97 and 1.06-0.12 respectivelly. (Zima et al., 2010). It is known that *P. tomentosa*'s leaf (1104,908 µmolTE g) and flower (223,280 µmolTE g) extracts have a sweeping effect on the DPPH radical (Uğuz and Kara, 2019). In a different study of the same species, IC50 value of DPPH radical scavenging effect was determined as 0.025 ± 0.001 mg mL. $TEAC_{ABTS}$ value was calculated as 0.821 ± 0.013 mM Trolox eq. mg and FRAB value as 1.647 ± 0.018 mM FeSO4 eq. mg (Jo and Kim, 2019). The components of the flower extract of *P. tomentosa* were separated using ethanol elution and it was determined that these components have strong antioxidant properties (Meng et al., 2014). DPPH radical scavenging effect of *P. coreana*'s shell using 50°C hot water and 25°C methanol was %32.51 and %87.22, respectively (Lee and Jeong, 2013). The percentage of DPPH scavenging inhibition percentages at concentrations 70 µl ml, 35 µl ml, 17.5 µl ml, 8.75 µl ml and 4.375 µl ml of the oil obtained from the seed of *Ceplararia syriaca* (L) was calculated 9.27 ± 8.16, 7.4 ± 3.79, 8.79 ± 0.58, 2.06 ± 1.57 and 8.7 ± 4.98, respectively (Atalan et al., 2020). IC50 values of DPPH radical scavenging effect of *Gypsophila laricina*,

Centaurea aphrodisea, *Centaurea polyclada* and *Limoniopsis davisii* were reported as 1.51, 2.11, 10.7 and 0.48 mg ml, respectively (Tozyılmaz et al., 2020). When we compare the obtained results with other results in the literature, it is seen that the antioxidant effect of *P. tomentosa* is higher than some plant species and lower than others. Because the concentrations used affect the study results.

Cytotoxic Effect

The cytotoxic effects of different concentrations of hexane, ethanol and methanol extracts of *P. tomentosa* against the MDA-MB-231 cell line at 540 nm wavelength are shown in Table 3.

Table 3. Cytotoxic effect of *P. tomentosa* at 540 nm wavelength against MDA-MB-231 cell line
Çizelge 3. P. tomentosa'nın MDA-MB-231 hücre hattına karşı 540 nm dalga boyundaki sitotoksik etkisi

	1/1000	1/2000	1/4000
Doxorubicin *(Doksorubisin)*	0.0982	0.0982	0.0982
(-) Control *((-)Kontrol)*	0.4395	0.4395	0.4395
P.tomentosa-H	0.241	0.633	0.4665
P. tomentosa-E	0.3712	0.7202	0.5287
P. tomentosa-M	0.3807	0.9792	0.6252

P. tomentosa-H: Hexane ectract of *P. tomentosa*; *P. tomentosa*-E: Ethanol ectract of *P. tomentosa*; *P. tomentosa*-M: Methanol ectract of *P. tomentosa*

According to the results obtained, the hexane, ethanol and methanol extracts of *P. tomentosa* showed the best cytotoxic effect at a concentration of 1/1000 against the MDA-MB-231 cell line at a wavelength of 540 nm. The cytotoxic effects of these extracts were determined as 0.241, 0.3712 and 0.3807, respectively. However, it has been observed that 1/2000 and 1/4000 concentrations of *P. tomentosa*'s hexane, ethanol and methanol extracts have no cytotoxic effects compared to control (Table 3).

In the cytotoxicity study of the active component isolated from *P. tomentosa* against HEPG2, A-549 and MCF-7 cell lines, IC50 values were reported as 14.5, 68.4 and 3.5 µg l*104, respectively (Ali et al., 2019). Some flavanoids isolated from *P. tomentosa* have shown different levels of cytotoxic effect against human erythro-leukemia K562 cells. In especially, it was determined that diplacone shows the best cytotoxic activity with the IC50 value of 4.4 µM (Smejkal et al., 2008). In the cytotoxic study of different concentrations of the same species (25, 50, 100, 200 µg mL) against the RAW264.7 cell line, it was observed that it did not affect cell viability at concentrations of 200 µg mL or less and was non-toxic (Jo and Kim, 2019).

CONCLUSION

Since plants are more frequently used in pharmacology in recent years, it is medically important to be preferred as natural agents in the treatment of diseases. For this purpose, we think that *P. tomentosa* may be a natural antibiotic or a therapeutic agent. Espesically, we anticipate that its antimicrobial, antioxidant and cytotoxic effects may be due to of the flavonides that it contains. The better understanding of the role of *P. tomentosa* componnents in medicine reqires further studies for upcomimg years.

Conflict Of Interest

The authors declared no conflict of interest.

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