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ARAŞTIRMA MAKALESİ **RESEARCH PAPER**

Biological Activity of *Laurus nobilis* L. Leaf and Fruit Extract

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Abstract: The leaves and fruits of *Laurus nobilis* L. are employed in pharmaceutical applications due to their various activities including antioxidant, antimicrobial and anti-inflammatory properties. The objective of the present study was to investigate the antimicrobial, anti-quorum sensing, cytotoxicity, and antiviral activity of the *Laurus nobilis* L. leaf and fruit extract, which was prepared using 70% ethanol. This study was conducted in the Department of Medical Microbiology, Faculty of Medicine, Karadeniz Technical University, with Laurel leaves and fruits collected from Trabzon province in the Black Sea region. The antimicrobial activity was investigated using the agar well method. A variety of bacterial and fungal strains were employed, including Gram-negative and Gram-positive bacteria as well as two fungal species. The anti-quorum sensing, antibiofilm and anti-swarming activities were investigated using the *Chromobacterium violaceum* ATCC 12472 and *Pseudomonas aeruginosa* PAO1 strains. The cytotoxic effect of ethanol extract prepared from the leaves and fruit of the *Laurus nobilis* L. plant on Vero, A549 and MDA-MB-231 cell lines was investigated using MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide) method. The antiviral effect of the extracts on HSV-1 was investigated using MTT method. The antimicrobial and quorum sensing activity were determined to be moderate. It was established that the leaf and fruit extracts of *Laurus nobilis* L. used in the study demonstrated antiproliferative and antiviral effects in a dose-dependent manner. Further investigation of the Laurel plant is required, utilizing different solvents.

Keywords: Cytotoxicity, HSV-1, antimicrobial, *Laurus nobilis*, quorum sensing.

Laurus nobilis L. Yaprak ve Meyve Özütlerinin Biyolojik Aktivitesi

***Sorumlu yazar:**
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Öz: *Laurus nobilis* L.'nin yaprak ve meyveleri antioksidan, antimikrobiyal ve anti inflamatuar gibi çeşitli aktiviteleriyle farmasötik uygulamalarda kullanılmaktadır. Bu çalışmada %70 etanol ile hazırlanan *Laurus nobilis* L. yaprak ve meyve ekstraktının antimikrobiyal, anti-quorum sensing duyarlılığı, sitotoksisitesi ve antiviral aktivitesinin araştırılması amaçlandı. Bu çalışma Karadeniz bölgesinde yer alan Trabzon ilinden toplanan Defne yaprak ve meyveleri ile Karadeniz Teknik Üniversitesi Tıp Fakültesi Tıbbi Mikrobiyoloji Anabilim Dalında gerçekleştirildi. Antimikrobiyal aktivite agar kuyucuk yöntemiyle araştırıldı. Dört adet gram negatif, beş adet gram pozitif bakteriler ve iki adet mantar türü kullanıldı. *Chromobacterium violaceum* ATCC 12472 ve *Pseudomonas aeruginosa* PAO1 suşları anti-quorum sensing, anti biyofilm ve anti-swarming aktiviteleri için kullanıldı. *Laurus nobilis* L. bitkisinin yaprak ve meyvesinden hazırlanan etanol ekstraktının Vero, A549 ve MDA-MB-231 hücre hatları üzerindeki sitotoksik etkisi MTT yöntemi ile araştırıldı. Ekstraktların HSV-1 üzerindeki antiviral etkisi MTT yöntemiyle araştırıldı. Antimikrobiyal ve quorum sensing aktivitesinin orta düzeyde olduğu belirlendi. Araştırmada kullanılan *Laurus nobilis* L. yaprak ve meyve ekstraktlarının doza bağlı olarak antiproliferatif ve antiviral etki gösterdiği anlaşıldı. Defne bitkisinin farklı çözücüler kullanılarak daha detaylı araştırılması gerekmektedir.

Anahtar kelimeler: Sitotoksisite, HSV-1, antimikrobiyal, *Laurus nobilis*, quorum sensing.

INTRODUCTION

In recent years, rapidly increasing antibiotic resistance and the inadequacy of combined antibiotic treatments have caused pathogenic bacteria to become a major threat to public health. Multiple resistance profiles of microorganisms have led researchers to investigate alternative methods for treatment and prevention of diseases. Another problem that is as dangerous as antibiotic resistance for today and the future is cancer. However, in recent years, new anti-cancer drugs have been introduced to the market, approximately half of which are derived from natural sources (Abu-Dahab et al., 2014). Natural compounds obtained from flowering plants are known to play an important role in cancer chemotherapy. The use of plants in treatment is a common practice from past to present. Especially the use of medicinal plants is increasing. Although many studies on medicinal plants have been published in the literature, there are still many plants that need to be researched (Ahmad et al., 2022). Laurel is frequently consumed as a spice in the Turkey. The plant, whose leaves are often used especially in raw form and as a spice, is one of the aromatic plant species that has become popular again in traditional medicine and in the pharmaceutical, agricultural food and cosmetic industries. Increasing demand for products containing laurel leaf has significantly increased its global production (Chaaben et al., 2015). Laurel (*L. nobilis*, family *Lauraceae*) is an evergreen tree (Hanif et al., 2019). The plant has been preferred in traditional medicine for many years thanks to its various pharmacological properties, including antimicrobial, antioxidant, anticancer, insecticidal, and antifungal (Nabila et al., 2022; Zibi et al., 2022). The homeland of the plant is the southern Mediterranean region. Due to the aromatic properties of its leaves, it is commercially produced in Algeria, Turkey, Morocco, Portugal, Spain, Italy, France and Mexico. It is often seen as an ornamental plant in Europe and the United States (Guenane et al., 2016). *L. nobilis*, due to its phytochemical compounds (Khodja et al., 2021) and its extensive use in the treatment of various neurological pathologies, dermatological and urological treatments, as well as gastrointestinal diseases such as epigastric bloating, digestive upset, flatulence, belching (Khodja et al., 2020) rate of research has increased rapidly in recent years.

L. nobilis, commonly known as bay laurel, has been the subject of various studies exploring its potential biomedical properties. Research has indicated that essential oils derived from *L. nobilis* exhibit antiviral activity against viruses such as SARS-CoV-1 (Roviello & Roviello, 2021). Additionally, studies have highlighted the diverse pharmacological activities of terpenoids found in Laurus nobilis, including anti-inflammatory, antidiabetic, antifungal, antibacterial, immunomodulatory, and cytotoxic properties (Boniface et al., 2023). Furthermore, *L. nobilis* has been found to possess antiviral activity against severe acute respiratory syndrome (SARS)-associated coronaviruses (Autiero & Roviello, 2023).

Moreover, *L. nobilis* has shown promise in cancer research, with reports of its potential antineoplastic effects. Compounds and extracts from *L. nobilis* have demonstrated activity against human papillomavirus (HPV)-transformed cell lines (Medeiros-Fonseca et al., 2018). Additionally, sesquiterpenoids isolated from Laurus nobilis have exhibited cytotoxicity against ovarian cancer cell lines (Bruno et al., 2013). Furthermore, *L. nobilis* leaf extracts have been evaluated for their cytotoxic properties, showing potential in inhibiting cancer cell proliferation (Kivçak & Mert, 2002).

Within the scope of this study, *L. nobilis* leaf and fruit extracts were screened for their anticancer, antiviral, antimicrobial and anti-quorum sensing properties.

MATERIAL AND METHOD

Preparation of laurel fruit and leaf extracts: Laurel fruits and leaves were dried before processing. Laurel extracts were prepared using the macerate method (Saliha et al., 2020).

Antimicrobial activity: *Bacillus cereus* (ATCC 14579), *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 25923), *Mycobacterium smegmatis* (ATCC 607), *Chromobacterium violaceum* (ATCC 12472), *Klebsiella pneumoniae* (ATCC 13883), *Salmonella typhimurium* (ATCC 14028), *Pseudomonas aeruginosa* (ATCC 27853), *Acinetobacter haemolyticus* (ATCC 19002) *Candida albicans* (ATCC 10231) and *Candida parapsilosis* (ATCC 22019) were used. The effect of extracts on microorganisms was investigated by the agar well method. For other microorganisms, Mueller Hinton Broth-II was used. Brain Heart Infusion Broth was used for M. smegmatis when determining the Minimum Inhibitory Concentration (MIC) (Saliha et al., 2020). MIC values of Candida were determined using RPMI 1640 with 0.20% glucose (Giske et al., 2022). To determine the Minimum Bactericidal Concentration (MBC) value, 50 µL was taken from the wells at and before the MIC and cultured on agar plates (Gür, 2016).

Anti-quorum sensing activity: The study was carried out using *Chromobacterium violaceum* ATCC 12472 bacteria. Firstly, the Sub-MIC values of the extracts were determined. For the experiment, an overnight culture of *C. violaceum* 12472 was prepared in a shaking incubator. Then, 50 µL of fresh *C. violaceum* culture was taken and added to soft Luria Bertani agar. The vortexed mixture was added to the previously prepared LB petri dishes. Wells with a diameter of 6 mm were opened on the petri dish. 50 µL of Sub-Mic concentrations of *L. nobilis*

fruit and leaf extracts were added to the opened wells. Values where there was growth around the wells, but no purple color was seen were considered positive for violacein suppression (Saliha et al., 2020).

Anti-swarming activity: Swarming activity of *L. nobilis* fruit and leaf extracts was determined using *P. aeruginosa* PAO1. First of all, Sub-MIC concentrations were determined and values below these concentrations were used in the study. The concentrations added to 5 mL LB soft agar medium were vortexed and added to the previously prepared LB agar petri dishes. A colony of bacteria was planted in the middle of the petri dishes with the help of a toothpick (Üreyen Esertaş et al., 2022). The next day, activity determined by comparing the colony morphology in petri dishes to which extract is added, with PAO1 colonies to which extract is not added.

Anti-biofilm activity: *P. aeruginosa* PAO1 will be used for antibiofilm activity testing. LB medium, PAO1 and *L. nobilis* extracts were added together to each well of flat-bottomed microplates. After one night incubation, the plate was washed with distilled water. Ethanol was added last to the plates treated with crystal violet. To determine biofilm formations, the plates were measured in a spectrophotometer at a wavelength of 570 nm (Saliha et al., 2020; Truchado et al., 2009).

Cytotoxicity of the Extracts: The cytotoxicity of the extracts was investigated on lung adenocarcinoma cell line (A549), breast cancer cell line (MDA-MB-247), and normal epithelial cell line (Vero). All cell lines from Karadeniz Technical University, Medical Microbiology Department culture collection, originally obtained from American Type Culture Collection (ATCC, USA) were used in the study. The MTT assay is a colorimetric technique to assess cell viability and proliferation. Metabolically active cells convert the yellow MTT dye into purple formazan crystals. The intensity of the purple color, measured by a spectrophotometer, correlates with the number of viable cells. MTT assay was performed as described in Cora et al. (2023) to determine the cytotoxicity of the extracts on cell lines (Cora et al., 2023).

Antiviral activity: The antiviral activity of the extracts against HSV-1 was analyzed using MTT method described in Cora et al. (2023) (Cora et al., 2023). The HSV-1 Wal strain from the virus collection at Karadeniz Technical University, originally obtained from the University of Sheffield (England) was included in the study. After Vero cells were infected with virus at a concentration of 1 TCID50, extracts were added to wells. Three wells were used for each concentration. 25-100 µg/mL concentrations of leaf extract, and 100-400 µg/mL concentrations of fruit extract that did not affect Vero cells were included in the study. Acyclovir was used as a positive control, and wells containing virus-infected cells were used as negative control. IC_{50} and selectivity indexes of the extracts were calculated.

Statistical Analysis: Results were presented as mean values and standard error (mean±SE). Data were tested using GraphPad 9.0 (GraphPad Software, Inc., La Jolla, CA, USA). Statistical analysis of the results was based on chi-square test. Significant differences were statistically considered at the level of $p<0.05$ otherwise given.

RESULTS AND DISCUSSION

Antimicrobial activity results: The results of antimicrobial activity of *L. nobilis* extract show that it has activity against microorganisms (Table 1). When the zone diameters and MIC values of these microorganisms are examined, it is seen that the antimicrobial activity of the extract is at a mostly susceptible level. (Table 2)

Table 1. Antimicrobial activity results zone (mm).

Microorganisms	*L. nobilis* L. fruit	*L. nobilis* L. leaf
B. cereus	20.0±1.0	18.33±2.08
C. violaceum	21.0±1.0	19.0±0.0
S. aureus	21±0.0	19.0±0.0
B. subtilis	18.33±2.08	13.66±0.57
E. faecalis	18.66±0.57	11.33±2.08
M. smegmatis	25.33±2.08	24.66±0.57
C. albicans	27.66±0.57	24.66±0.57
C. parapsilosis	23.33±2.08	21.33±2.08

Table 2. MIC/MBC results of the extracts (ug/mL).

Microorganisms	*L. nobilis* L. fruit	*L. nobilis* L. leaf
B. cereus	500/1000	500/1000
C. violaceum	500/1000	500/1000
S. aureus	500/1000	500/1000
B. subtilis	500/1000	1000
E. faecalis	500/1000	1000
M. smegmatis	500/1000	500/1000
C. albicans	250/500	500/1000
C. parapsilosis	500/1000	500/1000

MIC; Minimum Inhibition Concentration, MBC; Minimum Bactericidal Concentration

Anti-quorum sensing activity: It was determined that *L. nobilis* fruit and leaf extract suppressed violacein pigment, one of the quorum sensing steps (Table 3).

Table 3. Quorum sensing results.

	***C. violaceum* ATCC 12472**
L. nobilis L. fruit	+/-
L. nobilis L. leaf	+/-
Positive control (Vanilin)	+

Anti-swarming activity: It was determined that the extracts did not show anti-swarming activity.

Anti-biofilm activity: It was determined that the extracts did not show anti-biofilm activity.

Anti-cancer activity results: It was determined that the *L. nobilis* L. leaf extract had cytotoxic effects on Vero, A549 and MDA-MB-231 cell lines at concentrations of 200 µg/mL, 400 µg/mL, and 100 µg/mL, respectively. On the other hand, it was determined that *L. nobilis* L. fruit extract had no effect on Vero and A549 cell lines but had a cytotoxic effect on MDA-MB-231 cell line at concentration of 100 µg/mL and above. The cytotoxic effect of the extracts was summarized in Figure 1a and

Figure 1b. The IC_{50} values and selectivity indexes of the extracts were calculated and summarized at Table 4. The leaf and fruit extracts of *L. nobilis* L. used in the study were observed to have a dose-dependent anti-proliferative effect

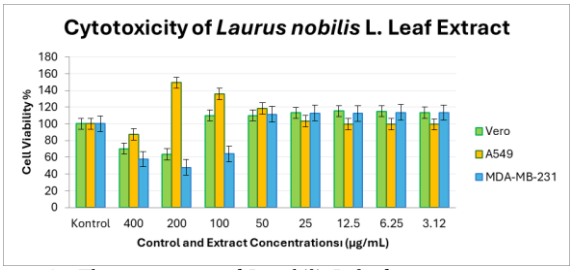

Figure 1a. The cytotoxicity of *L. nobilis* L. leaf extract.

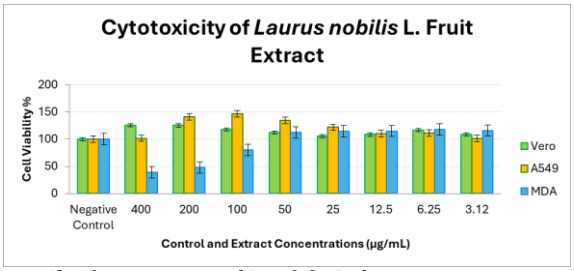

Figure 1b. The cytotoxicity of L. nobilis L. fruit extract.

Table 4. IC_{50} results and selectivity indexes of the extracts.

	L.nobilis L. Leaf Extract		*L.nobilis* L. Fruit Extract	
	IC_{50}	Selectivity Index	IC_{50}	Selectivity Index
Vero	479.4 µg/mL		1177.2 µg/mL	
A549	181.1 µg/mL	2.6	332.4 µg/mL	3.5
MDA-MB-231	341.4 µg/mL	1.4	291.9 µg/mL	4.0

Antiviral activity results: It was observed that the leaf extract did not have antiviral activity, while the fruit extract showed antiviral activity at 200 µg/mL and 400 µg/mL concentrations (Figure 2a, and 2b).

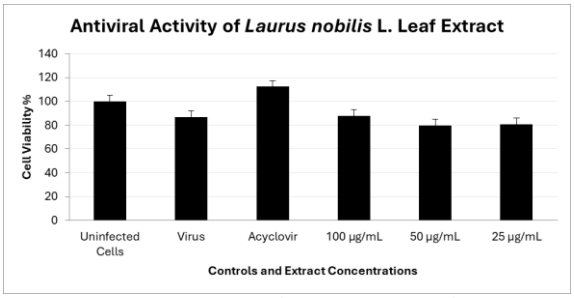

Figure 2a. The antiviral activity of the L. nobilis L leaf extract on HSV-1.

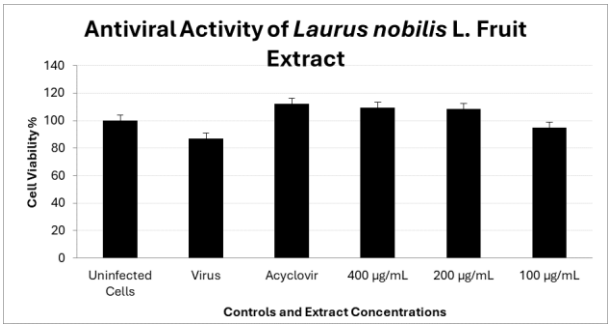

Figure 2b. The antiviral activity of the L. nobilis L fruit extract on HSV-1.

DISCUSSION

The studies show that the type of solvent used in *L. nobilis* extraction has a significant impact on antibacterial activity. Waghmare and Kalyane (2023) showed in their study that *L. nobilis* ethanol extract was more successful than other solvents (Khodja et al., 2023). Similar to the current study, Santos et al. (2008) determined that *L. nobilis* leaves had moderate activity against *Staphylococcus aureus*, *Proteus mirabilis* and *Escherichia coli* bacterial strains with values of 100 ≤ MIC ≤ 500 µg/mL.

In antimicrobial studies, the diameter of the inhibition zone is a crucial parameter used to evaluate the effectiveness of various substances against different microorganisms. The size of the inhibition zone is indicative of the potency of the antimicrobial agent. For instance, a larger diameter of the clear zone indicates a stronger inhibitory effect, while a smaller diameter suggests a milder effect (Sari et al., 2023). The assessment of antimicrobial activity often involves measuring the diameter of the inhibition zone after a certain incubation period (Akçay et al., 2010). This measurement helps in categorizing the strength of the antimicrobial activity, with different ranges of zone diameters corresponding to varying levels of inhibitory power (Sari et al., 2023).

The diameter of the inhibition zone can vary depending on the substance being tested and the microorganism under study. For example, in a study evaluating the antimicrobial activity of a medicinal plant extract, the extract exhibited different inhibition zone diameters against gram-positive and gram-negative bacteria compared to a standard antibiotic (Penu et al., 2020). Similarly, in another study on the antimicrobial effects of essential oils, the zone diameter was used to determine the antimicrobial activity of thyme against *S. aureus* (Canberi et al., 2020). According to Zone Diameter Interpretive Chart, more than 17 mm diameter can be classified as “Susceptible” (Jonasson et al. 2020).

In recent years, studies have focused on developing of anti-pathogenic agents to control bacterial

infections by blocking the communication between microorganisms. Communication between bacteria occurs through chemical signaling molecules known as autoinducers (Siehnel et al., 2010). Most pathogenic microorganisms use QS mechanisms to promote the production of virulence factors. Therefore, blocking QS is seen as an essential approach to control bacterial virulence and antimicrobial resistance, and research is rapidly increasing (Hong et al., 2012). Illustration of theories regarding quorum sensing inhibition and screening programs for new compounds with this activity have led to a recent resurgence in popularity of plant extracts in general and aroused scientific interest (Vattem et al., 2007). Ines Molina et al., (2020) investigated various biological activities of *L. nobilis* leaves in their study and determined partial biofilm activity on food pathogenic microorganisms (Molina et al., 2020). In the study, biofilm activity of the extracts on *P. aeruginosa* could not be determined. It is thought that biofilm activity should be tested on different strains. Loizzo et al., (2008) tested the oil of *L. nobilis* fruit on HSV-1 and SARS-CoV and determined an interesting activity on HSV-1 with an IC50 value of 60 mg/mL (Loizzo et al., 2008). Al-Shuhaib et al., (2023) suggested in their study that artecanin obtained from *L. nobilis* can be used as a potential natural inhibitor that can be used to block or at least counter the invasion of SARS-CoV-2 (Al-Shuhaib et al., 2023). Abu-dahab et al., (2014) emphasize in their study that *L. nobilis* is a potential natural agent in the treatment of breast cancer. They also report that, compared to unstimulated basal cells, both fruits and leaves of *L. nobilis* induce a significant enrichment in cytoplasmic mono- and oligonucleosomes after putative induction of programmed MCF7 cell death (Abu-Dahab et al., 2014). However, these studies were generally carried out with solvents such as water, ethanol, butanol, ethyl acetate and chloroform. A single solvent was used in the study, which is thought to be the main reason for the low activity. The study also allows methanol solvent results to be included in the literature.

CONCLUSION

The choice of solvent significantly influences the antibacterial efficacy of *Laurus nobilis*, with ethanol extracts showing superior activity. Antimicrobial effectiveness varies with the substance and microorganism tested, highlighting the importance of careful experimental design. Recent studies focus on the plant's potential in quorum sensing inhibition, antiviral activity, and cancer treatment, particularly breast cancer. However, reliance on a single solvent in many studies may limit observed bioactivity. Future research should explore a wider range of solvents, such as methanol, to better understand and utilize the therapeutic potential of *L. nobilis*.

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