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Anti-Quorum Sensing Activity of *Vitis vinifera* L. Seed Extract on Some Bacteria: A Greener Alternative Against Antimicrobial Resistance

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Abstract

In the present study, the seed extract of *Vitis vinifera* L. (grape) prepared with the methanol-ethanol mixture (volume ratio of 1:1) was evaluated for antibacterial activity on some Gram-positive and Gram-negative strains. In addition, the activity of the extract on the production potential of Quorum Sensing (QS)-dependent virulence factors on *Pseudomonas aeruginosa* PAO1 and *Chromobacterium violaceum* was investigated. The phytochemical analysis resulted in the identification of 23 phenolic phytochemicals; epicatechin, catechin and *p*-hydroxybenzoic acid were determined as the major components in the extract, respectively. The mode of action for the anti-QS activity was explored by molecular docking. The binding affinity of the three major phytoconstituents towards LasR and CviR was determined. Computational analysis demonstrated that the three components (epicatechin, catechin, *p*-hydroxybenzoic acid) could bind to LasR and CviR. The binding affinity towards LasR was higher than CviR. Hence, the activity of the extract on *P. aeruginosa* and *C. violaceum* could result from the competitive inhibition of LasR and CviR by the major components, respectively. Considering the literature and the computational analysis, it is thought that the antibacterial and anti-QS activity of the seed extract may be related to the synergistic effect of the phenolic phytochemicals it contains.

Keywords Molecular docking · Phytochemical · QS · Virulence · *Vitis vinifera* L.

Introduction

The term "antibiotic resistance" encompasses defence demonstrated by bacteria to antibiotics (Sharma et al. 2005). The inexorable rise in levels of this resistance is associated with high health care costs and mortality rates. As the biggest challenge in the treatment of infectious diseases, antibiotic resistance is recognized as a major concern for public health at the global level and requires international approaches (Getahun et al. 2020). To combat this worldwide threat, understanding the resistance mechanisms of bacteria remains the key to scientific progress. Among these, the QS system associated with bacterial viru-

Data Availability If further information about this study is required please contact the authors.

Code availability Not applicable.

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lence is the most remarkable mechanism in recent decades (Medarametla et al. 2021).

QS is a regulatory communication mechanism that allows bacterial populations to coordinate their behaviors by regulating specific genes that can play important roles in bacteria such as biofilm formation and production of virulence factors (such as elastase and pyocyanin) and leads to the development of drug resistance in bacteria. Therefore, inhibition of this mechanism is being investigated as an alternative treatment strategy in drug discovery programs to overcome antibiotic resistance (Tonkin et al. 2021).

P. aeruginosa PAO1 is a medically important Gram-negative opportunistic rod that shows resistance to antibiotics and is classified as a major cause of nosocomial infections (Lyczak et al. 2000). This resistance results from the production of virulence factors and biofilm formation all under the control of the QS system (Pompilio et al. 2015). Therefore, inhibition of QS pathways is considered a promising strategy for the control of microbial pathogenesis. In fact, many pathogenic bacteria use this system, including *Stenotrophomonas maltophilia, Escherichia coli, Vibrio cholerae, Acinetobacter baumannii* and *C. violaceum*. Although rare, it has also been reported that *C. violaceum* cause lung infections and metastatic abscesses of the spleen, brain and lymph nodes.

With increasing microbial resistance against antibiotics and environmental conditions, applying natural products (especially extracts) could provide a promising means of treatment. It is now well known that grape seed is a rich source of polyphenol compounds. Therefore, its antimicrobial activity has been investigated. In a study, the antibacterial activities of grape seed extracts against 15 bacteria were investigated. All tested bacteria were inhibited by grape seed extracts using the agar-well diffusion method. There are regions in Italy where alcoholic beverages obtained from *V. vinifera* L. are used to treat diseases related to the digestive system. In addition, wine, vinegar, and spirit obtained from the plant extract are used as an ointment, poultice, and mouthwash in the Republic of Cyprus (Baydar et al. 2006; Insanu et al. 2021).

To date, bioactive compounds of plant-based natural products have provided new drug leads used for the treatment of various diseases, including bacterial infections, and the discovery of QS mechanism has triggered the searches for anti-QS phytocompounds (Zahin et al. 2010).

In the present research described here, we aimed to evaluate the antibacterial activity of the *Vitis vinifera* L. (grape) seed extract on some Gram-positive and Gram-negative strains. In addition, the effect of the grape seed extract on the production potential of QS-dependent virulence factors on *P. aeruginosa* PAO1 and *C. violaceum* was investigated. To the best of our knowledge, there is no published comprehensive study in the literature on these activities of grape seed. We hope the results of our study will shed light on the development of new anti-infective therapeutic agents.

Materials and Methods

Plant Material and Extract Preparation

The grapes whose seeds were used in the study were commercially supplied and identified as *Vitis vinifera* L. by the botanist. The seeds were separated from the succulent parts of the fruits manually, dried in shade at 25 °C for 5 days, and ground into powder by using a grinding machine (Waring 8011 EB). After that, 8.8 g of seed powder was subjected to ultrasonic extraction with 88 mL methanol-ethanol mixture (volume ratio of 1:1) for 45 min. The extract was filtered and the filtrate was evaporated to dryness at 36 °C using a rotary evaporator (Heidolph Hei-Vap Rotary Evaporator [Germany]). At the end of the process, the crude plant extract remaining in the flask was weighed and the amount recorded, then dissolved with dimethylsulfoxide (DMSO) and transferred to a vial.

Phytochemical Screening

The phytochemical analysis of the seed extract was carried out using the high-performance liquid chromatography (HPLC) technique. HPLC conditions were presented in Table 1.

Screening Seed Extract for Antibacterial Activity

In our study, some Gram-positive and Gram-negative strains obtained from the bacterial stock available (*P. aeruginosa* PAO1; *Bacillus cereus* ATCC 11778; *Enterococcus faecalis* ATCC 29212; *Staphylococcus aureus* ATCC 25923; Methicillin-Resistant *Staphylococcus aureus* (MRSA);

Table 1 Solvent gradient conditions with the linear gradient

	Time (min)	A (%)	B (%)
Detector: Photo Diode Array Detector (λ max. 278 nm) Autosampler: SIL-10AD vp System controller: SCL-10A vp Pump: LC-10AD vp Degasser: DGU-14a Column heater: CTO-10 A vp Column: Agilent Eclipse XDB C-18 (250 mm × 4.6 mm), 5 µm Column temperature: 30 °C Mobile phases: A: acetic–water (3:97 v/v), B: methanol Flow rate: 0.8 ml/dak	0	93	7
	20	72	28
	28	75	25
	35	70	30
	50	70	30
	60	67	33
	62	58	42
	70	50	50
	73	30	70
	75	20	80
	80	0	100
	81	93	7

ATCC 43300; *Enterobacter aerogenes* ATCC 13048; and *Escherichia coli* ATCC 25922) were used. Antibacterial effects of grape seed extract were tested on these strains using the agar-well method (Holder and Boyce 1994). Bacteria grown in Luria-Bertani (LB) medium at 37 °C overnight were prepared the next day according to 0.5 McFarland turbid value. A total of 100 µL of the bacterial suspension prepared in 0.5 McFarland turbidity was added into 5 mL soft agar (0.5% agar) and poured onto the Müller-Hinton agar medium prepared in Petri dishes. The wells were opened with the help of a 6-mm diameter glass pipette on the media that were left to dry for a while and 100 µL of the seed extract was added into the wells. Antibacterial activity was determined by measuring the zone diameters formed at the end of 24-h incubation at 37 °C. All experiments were repeated three times unless otherwise mentioned.

Screening Seed Extract for QS Inhibitory Activity

Biofilm Formation Assay

The effect of seed extract on biofilm formation was investigated on *P. aeruginosa* PAO1 strain using the crystal violet method (Önem et al. 2018; O'Toole 2010). In all, 10 µL of an overnight culture of PAO1 (Optic Density [OD, Radiant Power] at 600 nm = 0.05) was added to a 96-well microplate containing 160 µL of freshly prepared Luria–Bertani Broth (LBB) medium and 20 µL of the seed extract. The microplate was incubated at 37 °C for 48 h. After incubation, the culture on the plates was drained and washed three times with sterile water. By adding 125 µL aqueous solution of crystal violet (0.1%) to the wells, the biofilm layer was dyed for 30 min, then the paint was poured and the excess was washed with distilled water. A total of 200 µL of 95% ethanol was added and the reaction mixture was read spectrophotometrically at 570 nm. The reference PAO1 strain was used as a positive control in this experiment. The negative control was sterile LBB.

The following formula was used to determine the inhibition of biofilm formation:

$$\text{Inhibition rate } (\%) = \frac{(OD_{\text{in control}} - OD_{\text{in treatment}}) \times 100}{OD_{\text{in control}}}$$

OD Optic Density

Elastolytic Assay

The elastolytic activity of the extract was determined with the Elastin Congo Red (ECR) test according to the method of Ohman et al. (Ohman et al. 1980). This test helps to measure the elastase activity in the supernatant of bacteria culture using ECR as substrate. Elastase B degrades elastin and this causes the Congo red dye to be released into the supernatant. The activity is assessed by spectrophotometric quantification.

Adhering to the mentioned procedure, 100 µL of the extract was mixed with 10 mL LBB containing OD 0.05 at 600 nm PAO1 culture and left to incubate at 37 °C by shaking for 16–18 h. A total of 100 µL of the supernatant part of this culture was transferred to a tube and 900 µL ECR buffer was added on. This mixture was incubated at 37 °C for 3 h with shaking at 200 rpm. After incubation, the sample was centrifuged at 4500 rpm for 5 min. The supernatant of the sample was transferred to a cuvette and its optical absorption at 495 nm wavelength was read spectrophotometrically (BioTek-Epoch 2 Microplate Spectrophotometer). PAO1 culture and LBB were used as positive and negative controls, respectively.

Pyocyanin Inhibition Assay

The effect of the extract on pyocyanin pigment production was determined as described by Essar et al. (Essar et al. 1990). A total of 100 µL of plant extract were added to 10 mL of LBB medium and incubated at 37°C in a shaker incubator overnight. After the incubation period, 5 mL of chloroform was added to the medium and vortexed for 30 s. The sub-phase formed in the medium and separated from chloroform was transferred to tubes as 2 mL. In all, 1 mL HCl-water mixture (0.2 mol/L HCl) was added on it and once again vortexed for 30 s. The absorbance of the pink phase formed on the upper part of the tubes was recorded at 520 nm. Untreated PAO1 served as the positive control.

Inhibition of Violacein Production

In order to quantify violacein inhibitory activity of *V. vinifera* L. seed extract on *C. violaceum* 12472, spectrophotometric flask incubation assay was used (Choo et al. 2006). A total of 100 µL of plant extract were added to 5 ml LBB medium and incubated at 30 °C in a shaking incubator overnight. At the end of the incubation, 1 mL bacteria culture was centrifuged at 13,000 rev min^{-1} for 10 min. Then the supernatant was removed and 1 mL of DMSO was added on pellet and vortex for 30 s. After vortex again at 13,000 rev min^{-1} for 10 min, supernatant with violacein was read at 585 nm.

Statistical Analysis

The experiments were carried out in triplicate according to the randomized plot design and the data obtained were subjected to variance analysis using the JMP 8 packet statistics

program. Statistical differences were marked by the LSD multiple comparison test.

Molecular Docking

Molecular docking was performed with AutoDock Vina (Trott and Olson 2010). The crystal structure of LasR with PDB code of 6MWL, (Paczkowski et al. 2019) and the structure of CviR with PDB code of 3QP1 (Chen et al. 2011) was obtained from a protein data bank (PDB). The structures of the ligands were obtained from PubChem (Kim et al. 2021). Prior to docking, grid boxes that encompass the ligands bound in the structure of the proteins were determined. The protein structures obtained from a PDB were prepared by removing water, adding polar hydrogens, and assigning Gasteiger charges. Similarly, the ligands were prepared by adding polar hydrogens and assigning Gasteiger charges. Then, AutoDock Vina was run (Onem et al. 2021). Docking outcomes were visualized and analyzed with Biovia Discovery Studio.

Results

Results of Antibacterial Activity Test

According to the data obtained, while the extract showed different antibacterial effects on Gram-positive strains, no effect was observed on Gram-negative strains (Table 2).

Table 2 Antibacterial activity of the seed extract against bacterial pathogens tested using agar-well assay

Test bacteria	Zone of inhibition (mm)	
	Extract (16 mg/mL)	Standard (Gentamicin, 30 µg/mL)
S. aureus ATCC 25923	15	15
MRSA ATCC 43300	16	14
B. cereus ATCC 11778	15	18
E. faecalis ATCC 29212	11	16
E. aerogenes ATCC 13048	NE	NE
E. coli ATCC 25922	NE	NE
P. aeruginosa PAO1	NE	NE

NE noneffective

Confirmation of Anti-QS Activity

Fig. 1 presents the results of the antibiofilm formation assay. The extract inhibited biofilm formation of PAO1 by 38%.

The results of the elastolytic assay are given in Fig. 2. The percentage of elastase inhibition of the extract was calculated as 79%.

Results of the pyocyanin inhibition assay are shown in Fig. 3. The pyocyanin inhibition rate of the extract was found as 89%.

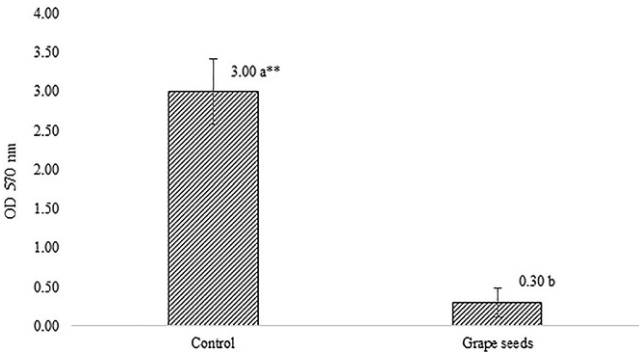


Fig. 1 Inhibition effect of seed extract on PAO1 biofilm (**The difference between averages with different letters is important, $P < 0.01$ [SD±])

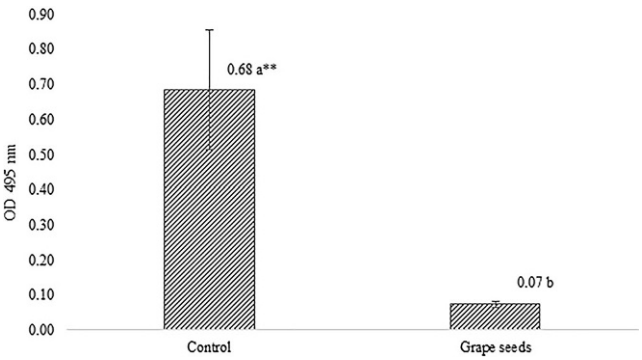


Fig. 2 The results of the elastolytic assay on PAO1 (**The difference between averages with different letters is important, $P < 0.01$ [SD±])

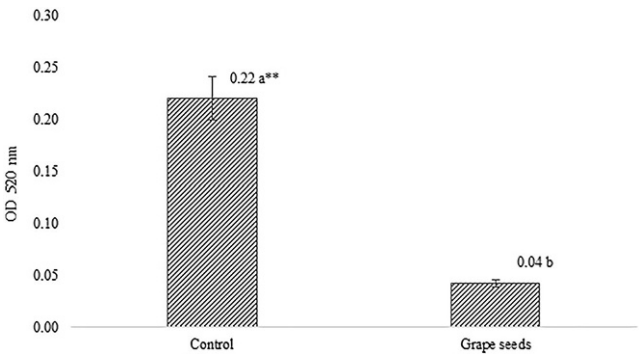


Fig. 3 The results of the pyocyanin inhibition assay on PAO1 (**The difference between averages with different letters is important, $P < 0.01$ [SD±])

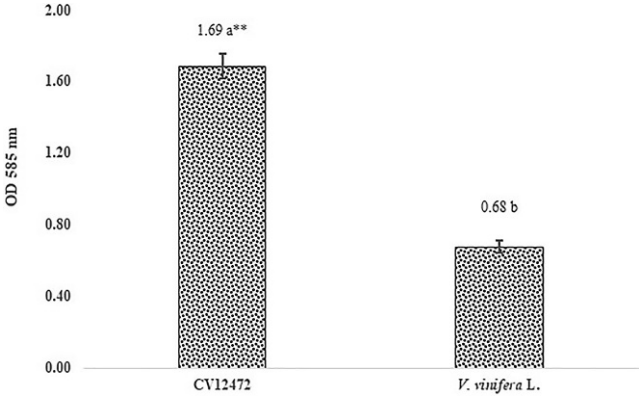


Fig. 4 Inhibition effect of extract on violet pigment of CV12472 ($P < 0.01$) (**The difference between averages with different letters is important, $P < 0.01$ [SD±])

Violacein Inhibition

As a result of the experiment in which the inhibition effect of violet pigment production by the *C. violaceum* 12472 with QS control was investigated with grape seed extract and 60% inhibition was determined at 50 mg concentration (Fig. 4).

Results of HPLC Analysis

The HPLC chromatogram of the grape seed extract (Fig. 5) shows the presence of 23 phenolic components, all of which are given in Table 3. Epicatechin had the highest concentration (2346 µg/mL), followed by catechin with a concentration of 1204 µg/mL, then *p*-hydroxybenzoic acid with a concentration of 414 µg/mL.

Molecular Docking

The mode of action for the activity of the extract on the QS system was investigated through molecular docking. For this purpose, the most abundant three phytochemical constituents (epicatechin, catechin, and *p*-hydroxybenzoic acid) were docked on LasR and CviR. The docking outcomes showed that these phytoconstituents had better interaction with LasR. The interactions of LasR with epicatechin and *p*-hydroxybenzoic were given in Fig. 6 and Table 4. The interaction of catechin with LasR was investigated in a previous study (Table 4) (Gürağaç Dereli et al. 2022).

The interactions of the three most abundant molecules were also compared with the interactions of the natural ligand of LasR, N-3-(oxododecanoyl)-l-homoserine lactone (OdDHL). The results were analyzed accordingly (Table 4).

The binding mode of epicatechin, catechin, and *p*-hydroxybenzoic acid with CviR was also studied. There were interactions of the three abundant molecules with the pro-

Table 3 Concentrations of the main phenolic compounds identified in the grape seed extract

Phytochemicals	Concentrations (µg/mL)	Retention time (min)
Gallic acid	49	5.41
Protocatechuic acid	n.d.	9.34
p-Hydroxybenzoic acid	414	14.60
Chlorogenic acid	203	16.17
Caffeic acid	160	18.84
Syringic acid	146	21.24
Vanillin	175	22.23
p-Coumaric acid	97	43.37
Ferulic acid	n.d.	30.23
Sinapic acid	n.d.	31.90
Benzoic acid	n.d.	37.42
p-Coumaric acid	97	26.06
Rosmarinic acid	n.d.	61.77
Cinnamic acid	n.d.	69.0
Catechin	1204	13.50
Epicatechin	2346	20.57
Hesperidin	n.d.	56.14
Eriodictyol	n.d.	63.76
Quercetin	210	72.94
Luteolin	n.d.	75.4
Kaempferol	76	77.13
Apigenin	n.d.	77.5

n.d. not detected

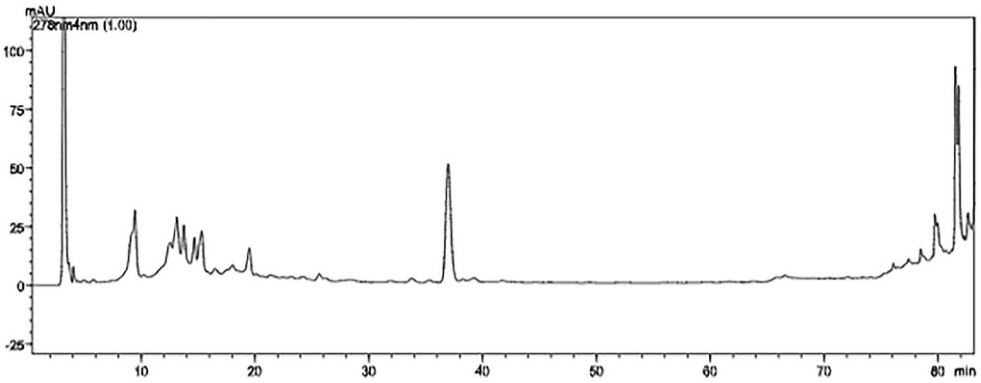


Fig. 5 High-performance liquid chromatography of grape seed extract

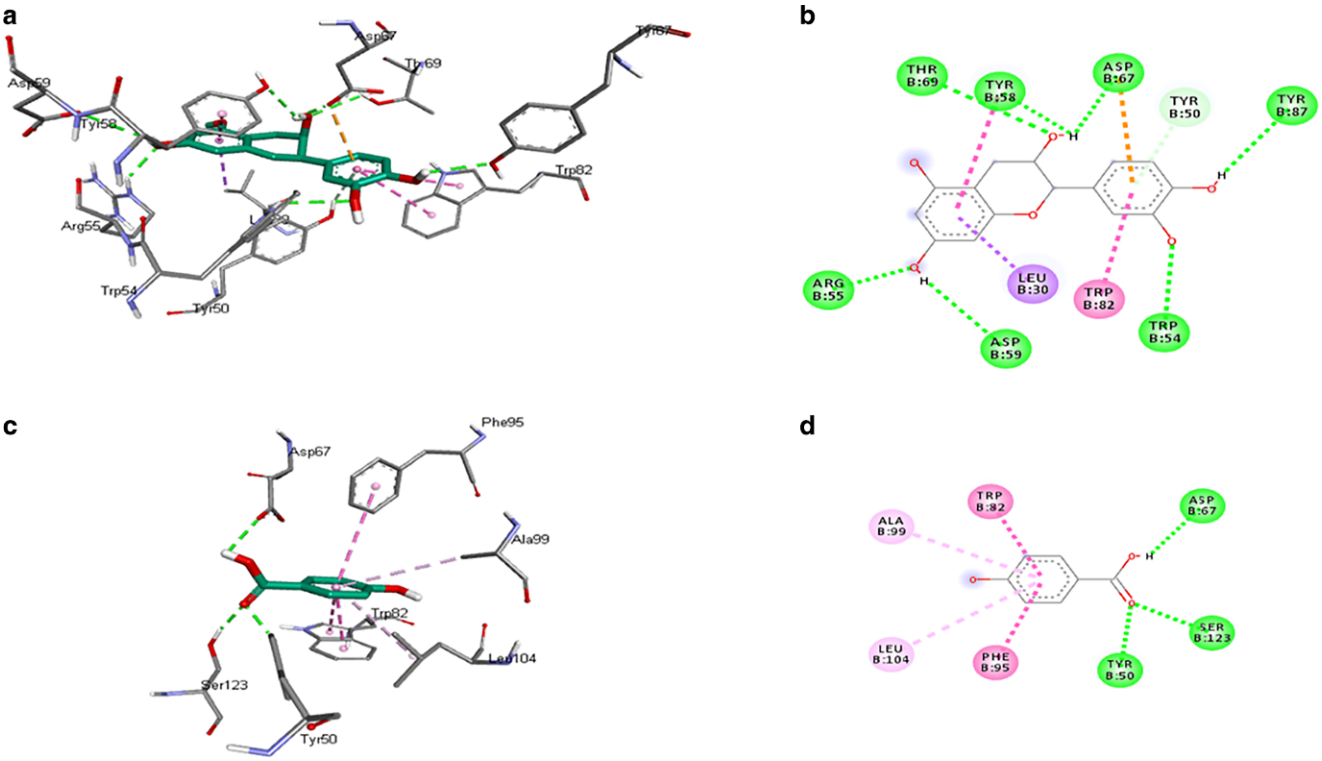


Fig. 6 Binding profile with LasR: **a** Three-dimensional (3D) binding of epicatechin, **b** two-dimensional (2D) binding of epicatechin, **c** 3D binding of *p*-hydroxybenzoic acid, **d** 2D binding of *p*-hydroxybenzoic acid

Table 4 Binding residues of the three most abundant components and the natural ligand

Ligands	Binding energy (kcal/mol)	Hydrogen bonding points	Other interaction points
OdDHL	–9.0	Thr69	Gly32, Ile46, Arg55, Tyr58
Epicatechin	–10.4	Trp54, Arg55, Tyr58, Asp59, Asp67, Thr69, Tyr87	Leu30, Tyr50, Tyr58, Asp67, Trp82
Catechin	–11.9	Thr69, Tyr87, Ser123	Leu30, Tyr58, Asp67, Trp82, Phe95, Ala99, Leu104
P-hydroxybenzoic acid	–8.1	Tyr50, Asp67, Ser123	Trp82, Phe95, Ala99, Leu104

tein. However, the binding ability of the ligands with CviR was found to be less than that of LasR (Fig. 7). The binding of the components was compared with its natural ligand, N-hexanoyl-L-homoserine lactone (C6-HSL). The binding energies of epicatechin, catechin, *p*-hydroxybenzoic acid, and C6-HSL were found to be –9.1 kcal/mol, –6.9 kcal/mol, –6.7 kcal/mol, –6.9 kcal/mol, respectively.

Discussion

Hospital infections caused by multi-drug resistant bacteria resulting from the overuse and misuse of antibiotics are a nightmare for physicians all over the world. The emergence of bacteria resistance to existing conventional antibiotics and the inadequacy of antibiotics in the treatment of infections caused by these types of bacteria indicate the urgent need for new strategies to develop effective therapeutic options (Saleem et al. 2010). The use of plants for medicinal purposes has been going on for thousands of years (Solecki 1975). They have formed the basis of many traditional medicine systems to date and continue to offer new hope to humanity in terms of treatment today (Jachak and Saklani 2007). Recently, the importance of phytochemicals to reduce bacterial virulence in *P. aeruginosa* has been realized and researches in this field have gained momentum. Grape plant *V. vinifera* L. is an economically and medicinally important member of the family Vitaceae. It is one of the most planted fruit plants all over the world and represents a precious resource of nutraceuticals and pharmaceuticals (Vivier and Pretorius 2002). Especially the leaves and seeds of the plant, the fruit of which is consumed as a nutritional supplement, have been the subject of scientific research. Recent studies have demonstrated that the seed part

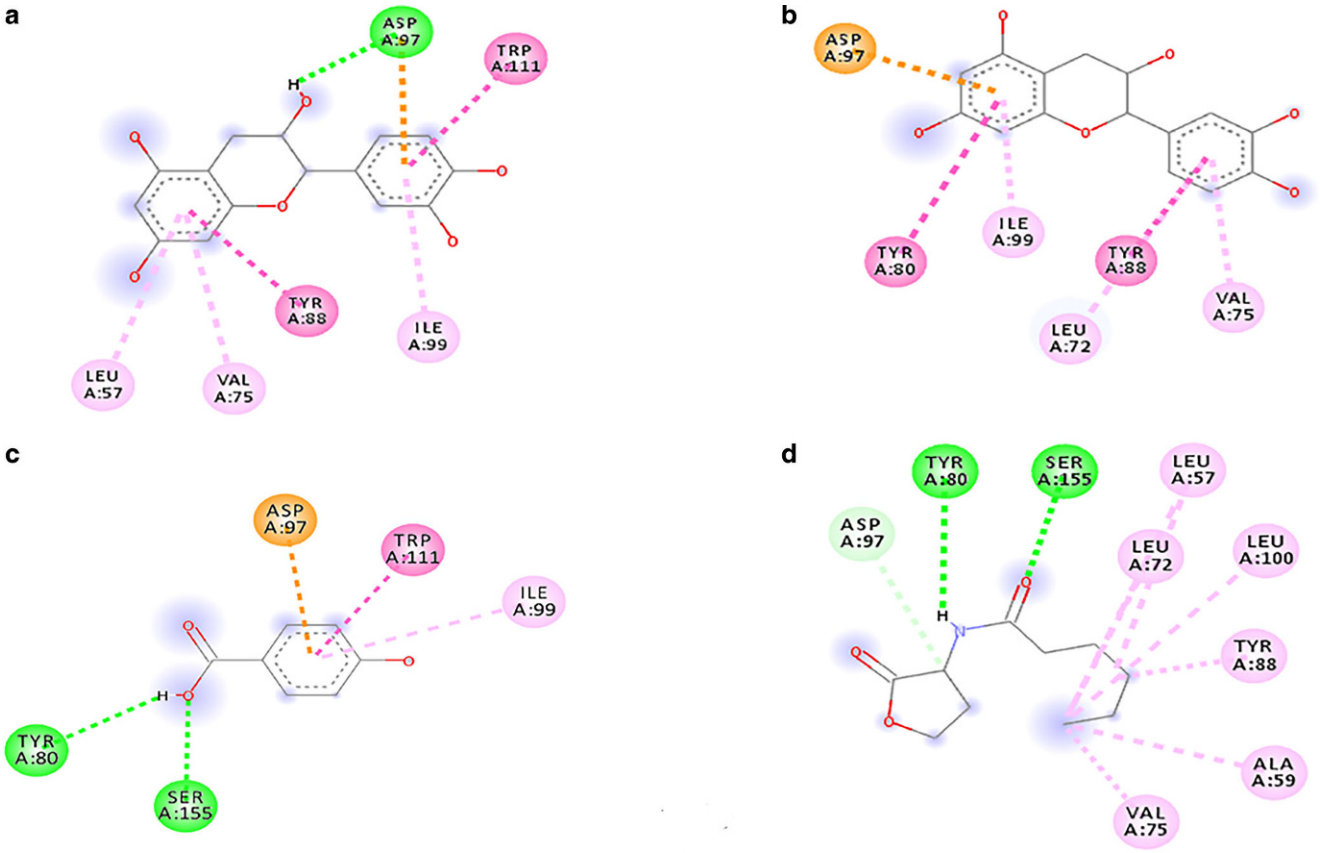
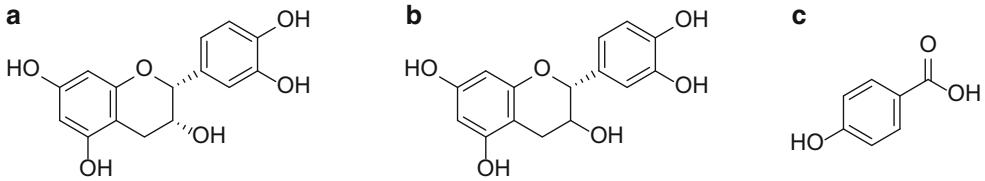


Fig. 7 Two-dimensional interactions with CviR: **a** epicatechin, **b** catechin, **c** *p*-hydroxybenzoic acid, **d** C6-HSL (in the figure, the color representation is: *green* conventional hydrogen bond, *orange* pi-ion, *pink* pi-pi, *lavender* pi-alkyl interactions)

Fig. 8 Chemical structures of determined major compounds in the *grape* seed extract: **a** Epicatechin, **b** catechin, **c** *p*-hydroxybenzoic acid



of the plant possesses a broad spectrum of pharmacological activities such as antioxidant, antidiabetic, cardioprotective, neuroprotective, hepatoprotective, anticancer, anti-inflammatory, antiviral, and antimicrobial activities (Insanu et al. 2021). The reports of the studies to determine the chemical content of seeds indicate the presence of large amounts of phenolic compounds, predominantly epicatechin, catechin, procyanidin, and gallic acid (Monagas et al. 2003). It has been shown that partially hydrophobic phenolic compounds in the seeds interact with the bacterial cell wall and lipopolysaccharide interfaces by reducing membrane stability and are directly related to antibacterial activity (Baydar et al. 2006). In the current study, grape seed extract was evaluated for both antibacterial and anti-QS activity. There is no other study in the literature so comprehensively investigating the effectiveness of grape seed against bacteria.

The results of the experiments carried out proved that the extract has antibacterial activity on the Gram-positive bacteria used in this study and the extract has inhibitory activity on the regulation of virulence and biofilm formation. Phytochemical analysis performed on the extract resulted in the identification of 23 phenolic phytocomponents, with epicatechin (Fig. 8a), catechin (Fig. 8b), and *p*-hydroxybenzoic acid (Fig. 8c) being determined as the major compounds in the extract.

The phenolic phytoconstituents have attracted scientific interest in terms of their diverse biological roles, including antibiotic and anti-QS activities. In a study by Vandeputte and colleagues, catechin was found to have inhibitory activity on elastase and pyocyanin production and biofilm formation by down-regulating QS gene expression in PAO1. On the other hand, it was determined that this compound had an inhibitory effect on pyocyanin production (Vandeputte

et al. 2010). In the study conducted by Lahiri and associates, it has been determined that catechin obtained from *Azadirachta indica* leaf extract is highly active in preventing dental biofilm, and this compound can be used in the treatment of chronic biofilm-associated infections (Lahiri et al. 2021). Furiga and coworkers proved that catechin and its epimer epicatechin inhibited the formation of multi-species biofilms composed of oral bacteria (Furiga et al. 2014, 2008).

In the phytochemical content analysis, epicatechin, catechin, and *p*-hydroxybenzoic acid were found to be the three abundant components of the grape seed. The anti-QS activity investigation demonstrated that the extracts were effective on both *P. aeruginosa* and *C. violaceum*. The experimental activity test results were explained through molecular docking. This was done by the docking of the three abundant components with LasR and CviR.

The molecular docking of epicatechin, catechin, and *p*-hydroxybenzoic acid with LasR revealed the high binding affinity of the phytochemicals; epicatechin in particular interacted with seven conventional hydrogen bonds. The interactions of the components were better than the interaction of the natural ligand, OdDHL. Furthermore, catechin and epicatechin had slightly lower binding energy than OdDHL. The three components had common interaction residues with OdDHL (Arg55, Tyr58, Thr69) (Fig. 6). The high binding affinity with similar binding points implicated that these components would inhibit the LasR by competitively interfering with the binding of the autoinducer, OdDHL. Therefore, the anti-QS activity on *P. aeruginosa* could be the result of the LasR inhibition.

The molecular docking of epicatechin, catechin, and *p*-hydroxybenzoic acid demonstrated that these components had binding affinity with CviR. However, the ability to bind to CviR was found to be lower than their binding affinity towards LasR. The three components exhibited better interaction with LasR in binding energy and interaction strength. These components had almost all the interactions of the natural ligand, C6-HSL (Leu57, Leu72, Val75, Tyr80, Tyr88, Asp97, Ser155) with CviR. The binding energies of the molecules were close to each other.

The components had less interaction than C6-HSL separately (Fig. 7). Together with this, the cumulative interactions of the three constituents were higher than C6-HSL. Hence, the anti-QS effect on *C. violaceum* might result from the inhibition of CviR by the constituents competitively. In the experimental study, grape seed extract was found to be more active on *P. aeruginosa* than *C. violaceum*. Similarly, in the computational study, the three phytoconstituents had a better binding affinity towards LasR than CviR. Hence, the computational analysis confirmed the outcomes of the activity study. As a result, considering the literature data and the computational analysis results, it is thought that the antibacterial and anti-QS activity of the grape seed extract may be due to the synergistic effect of the phenolic phytochemicals in its content. Hopefully, the outcomes of this study will provide new insight into the treatment of infectious diseases.

Author Contribution All authors participated in the development and design of the study. B.M. Ibrahim analyzed the antimicrobial activity data and prepared the manuscript. F.T. Dereli took part in data collection and read the article. E. Önem was involved in data collection, HPLC analysis of data, QS activity data, and statistical analysis. E. Arin was involved in data collection and analysis of data. M.T. Muhammed participated in the molecular docking description and read the article. All authors have read and approved the final version of the article.

Conflict of interest B.M. Ibrahim, F.T. Dereli, Y. Erzurumlu, E. Önem, E. Arin, and M.T. Muhammed declare that they have no competing interests.

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