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RESEARCH ARTICLE

Evaluation of the antibacterial activity of cultivated Caucasian whortleberry (*Vaccinium arctostaphylos* L.) against fish pathogens

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Abstract. Bacterial diseases are one of the major factors hampering aquaculture sustainability. Antibiotics are used widely to treat or prevent infectious bacterial diseases in aquaculture. However, because of growing problems of antibiotic resistance caused by the imprudent use of antibiotics, sourcing environmentally benign alternatives, such as herbal/medicinal plants, is now the focus of many researchers. Hence, in this study, a minimum inhibitory concentration (MIC) test with broth microdilution was performed to determine the in vitro antibacterial activity of an aqueous methanolic extract of cultivated Caucasian whortleberry (*Vaccinium arctostaphylos* L.) against various fish pathogens, i.e., *Yersinia ruckeri*, *Pseudomonas putida*, *P. luteola*, *Aeromonas salmonicida*, *A. hydrophila*, and *A. sobria*. The results revealed that the MIC values of the aqueous methanolic extract against *Y. ruckeri*, *P. putida*, *P. luteola*, *A. salmonicida*, and *A. hydrophila* were 8.75 mg mL^{-1}, while against *A. sobria* it was 2.19 mg mL^{-1}. This study indicated that the medicinal plant *V. arctostaphylos* L. can potentially be used against all the fish pathogens tested thanks to its various important bioactive compounds. However, to assess the potential of this plant, further in vivo studies should be carried out.

Keywords: Bioactive compounds, Bacterial diseases, Fish health management, Medicinal plant, Minimum inhibitory concentration

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Introduction

Global cultured food fish was estimated to be 82.1 million tons in 2020, indicating that aquaculture remains an important source of animal protein (Pradeepkiran 2019, FAO 2020) in response to the exponential growth of the human population (Tahiluddin and Terzi 2021). However, the expansion of intensive culture activities has resulted in disease outbreaks (Lafferty et al. 2015) and environmental pollution (Zhou et al. 2018). These have led to the decline of fish health and growth status from exposure to a diverse range of infectious agents and diseases; hence, losses of paramount economic growth are expected (Ramesh and Souissi 2018).

Bacterial fish pathogens, such as *Yersinia ruckeri*, *Pseudomonas putida*, *P. luteola*, *Aeromonas* *salmonicida*, *A. hydrophila*, and *A. sobria*, are ubiquitous, opportunistic, and generally infect both freshwater and marine/brackish fishes (Aydin et al. 1998, Tobback et al. 2007, Öztürk and Altınok 2014, Tahiluddin and Terzi 2021). Antibiotics are used widely in the treatment and prevention of infectious bacterial diseases in fish culture (Corum et al. 2020, Terzi et al. 2020). Occasionally, vaccines or bacteriophages also provide an opportunity to reduce the problem (Karga et al. 2020, Ture et al. 2022). However, antibiotics have some detrimental effects on the environment and animals (Terzi 2018, Terzi and Isler 2019), and vaccines are utilized for specific pathogens (Karga et al. 2020). Because of these, sourcing environmentally benign alternatives, such as the use of herbal/medicinal plants, is now the focus of many researchers (Özçelik et al. 2020, Terzi et al. 2021).

As the importance of medicinal plants has become clear, the extensive use of antibiotics in the aquaculture industry has been steadily decreasing (Li et al. 2022). Recently, medicinal plants have been tested in aquaculture as safe, eco-friendly substances to modulate the immune status of fishes, improve their growth performance, and inhibit diseases (Terzi et al. 2021, Tadese et al. 2022). Additionally, a large number of medicinal plants have shown excellent properties, such as antibacterial, antiviral, and antifungal activity, physiological support for digestive and immune systems, and hormonal balancing (Li et al. 2022). They are also important for aquaculture as they promote growth, stimulate appetite, and reduce stress, and as immunostimulants (Van Hai 2015, Tadese et al. 2022). They are also useful in assisting cultured animals to manage external stressors, including overcrowding, high environmental temperatures, and poor water quality (Tadese et al. 2022).

Caucasian whortleberry, *Vaccinium arctostaphylos* L., is a deciduous, perennial plant with edible purple-black to black berries that typically grows as a woody bush or shrub (Özgen et al. 2014). In Türkiye, this plant is predominantly distributed in the northeastern Black Sea region forests (Özgen et al. 2014), and it is of economic importance to the country (Bilgin et al. 2016c). *V. arctostaphylos* L. has a high content of anthocyanins (Latti et al. 2009) and phenolic compounds (Colak et al. 2016) and has a powerful antioxidant capacity (Özgen et al. 2014). This medicinal plant is popular and is utilized in Turkish medicine as an antihypertensive and antidiabetic agent (Baytop 1999). Currently, this medicinal plant is important in modern medicine as a remedy for cardiovascular diseases (Bakhshipour et al. 2019) and for diabetic patients (Kianbakht et al. 2013). People from the countryside gather its fruits for consumption and sell them on the streets (Ozkan et al. 2019). Previous studies indicated that *V. arctostaphylos* L. possesses antibacterial properties (Mahboubi et al. 2013, Mohammadi-Aloucheh et al. 2018, Bayrami et al. 2019, Khodadadi et al. 2021). Hence, testing its antibacterial property against fish pathogens is worth investigating. In this study, a minimum inhibitory concentration (MIC) test with the broth microdilution method was performed to determine the in vitro antibacterial activity of an aqueous methanolic extract of cultivated *V. arctostaphylos* L. against different fish pathogens, i.e., *Yersinia ruckeri*, *Pseudomonas putida*, *P. luteola*, *Aeromonas salmonicida*, *A. hydrophila*, and *A. sobria*.

Materials and Methods

Plant and Preparation of the Extract

The cultivated *V. arctostaphylos* L. was obtained from Rize, Türkiye. Aqueous methanolic extraction of the fruit was performed at the Research Laboratory of Fisheries Faculty, Kastamonu University, Türkiye using the method described by Bilen et al. (2016b). Briefly, the fruits of the plant were washed with deionized water and then dried. Then the dried fruits were powdered in a laboratory blender. A total of 50 g of powdered sample was percolated with 1 L methanol (40%) for three days and mixed twice daily by inversion. The mixture was filtered, and the solvent was concentrated in a rotary vacuum evaporator. The concentrate was dissolved in 25 mL of deionized water.

Determination of plant extract components

The bioactive components of the extract of *V. arctostaphylos* were determined using Gas Chromatography Mass Spectrometry (GC-MS) in the Central Research Laboratory of Kastamonu University according to Özkan et al. (2017).

Bacterial Strains

The *Yersinia ruckeri*, *Pseudomonas putida*, *P. luteola*, *Aeromonas salmonicida*, *A. hydrophila*, and *A. sobria* strains that were used in this study were isolated previously from the diseased rainbow trout (*Oncorhynchus mykiss* Walbaum)) (Terzi et al. 2020) and identified using conventional (morphological and biochemical analyses) and molecular methods (16S rRNA gene sequencing).

Minimum Inhibitory Concentration (MIC) Determination with Broth Microdilution

The broth microdilution method of the Clinical and Laboratory Standards Institute was used to determine the MICs of the extract against the fish pathogenic bacteria (CLSI 2018). The antibacterial activity of the extract was determined using 96-well plates. Twelve dilutions of fruit extract ranging from 140 to 0.07 mg mL^{-1} were prepared in Mueller Hinton Broth medium, and a total of 200 µL of each dilution per well was used for the MIC test. For the control, only medium and bacteria were prepared and added to 96-well plates. The plates were then placed in the incubator and kept at 25°C for 48 hours. The lowest concentration of extract that visibly inhibited bacterial growth was considered the MIC.

Ethical Statement

For this type of study, an ethical statement is not required since the study did not use animals.

Results

The bioactive components of the extracts are shown in Table 1.

Among the 32 different compounds found in the extract of *V. arctostaphylos* L. in the present study, 4,8,13-Cyclotetradecatriene-1,3-diol,1,5,9-trimethyl-12-(1-methylethyl)- (11.11%), 3.alpha.,5.alpha.-Cyclo-ergosta-7,9(11),22t-triene-6.beta.-ol (9.24%), 22,23-Dibromostigmasterol acetate (9.18%), 9-Octadecenethioic acid, 12-hydroxy-, S-t-butyl ester (6.60%), and Dodecane (4.82%) were the five dominant compounds based on peak area percentages.

MIC tests revealed that the MIC values of the aqueous methanolic extract for *Y. ruckeri*, *P. putida*, *P. luteola*, *A. salmonicida*, and *A. hydrophila* were 8.75 mg mL^{-1}, while for *A. sobria* it was 2.19 mg mL^{-1} (Table 2).

Discussion

The literature indicates that medicinal plants are now used widely in aquaculture to improve the growth and overall health status of cultured aquatic animals. For instance, mint, sage, and thyme oils used as feed supplements have been proven effective in improving the growth performance and antioxidant enzyme activities of rainbow trout (Sönmez et al. 2015). Tetra (*Cotinus coggyria*) provides immunostimulant effects to rainbow trout (Bilen et al. 2011). White mustard oil had a favorable effect on the overall health and growth of rainbow trout (Salem et al. 2022).

Medicinal plant extracts have been proven effective as protection against fish pathogens (Karga et al. 2020, Adeniyi et al. 2022). The antimicrobial properties of nettle (*Urtica dioica*), a medicinal herb, have shown disease resistance against *A. hydrophila* (Bilen et al. 2016a). Medicinal plants such as thyme (*Thymus vulgaris*), fenugreek (*Trigonella foenum graecum*), and rosemary (*Rosmarinus officinalis*) used as feed additives have resulted not only in improved hematological status and non-specific

Table 1
Bioactive components of cultivated Caucasian whortleberry (*Vaccinium arctostaphylos* L.) extract

Peak #	Area %	Components
1	11.11	4,8,13-Cyclotetradecatriene-1,3-diol,1,5,9-trimethyl-12-(1-methylethyl)-
2	9.24	3.alpha.,5.alpha.-Cyclo-ergosta-7,9(11),22t-triene-6.beta.-ol
3	9.18	22,23-Dibromostigmasterol acetate
4	6.60	9-Octadecenethioic acid, 12-hydroxy-, S-t-butyl ester
5	4.82	Dodecane
6	4.75	E,E,Z-1,3,12-Nonadecatriene-5,14-diol
7	4.55	Decane
8	4.47	Dotriacontane
9	4.34	Hexatriacontane
10	3.97	Tetracontane
11	3.75	2,4-Dimethyl-1-heptene
12	3.75	Tetradecane (CAS)
13	3.63	1-Heptanol, 2,4-diethyl-
14	3.39	9-t-Butyltricyclo[4.2.1.1(2,5)]decane-9,10-diol
15	2.69	Heptane, 2,5,5-trimethyl- (CAS)
16	2.61	9,12-Octadecadienoic acid (Z,Z)-, methyl ester (CAS)
17	2.44	Benzene, 1,3-bis(1,1-dimethylethyl)-
18	2.39	Hexadecane
19	2.00	2-Isopropyl-5-methyl-1-heptanol
20	1.93	Hexadecanoic acid, methyl ester (CAS)
21	1.77	Phenol, 2,2'-methylenebis[6-(1,1-dimethylethyl)-4-methyl-
22	1.20	Octacosyl acetate
23	1.09	Tetradecanoic acid, 5,9,13-trimethyl-, methyl ester
24	1.08	Methyl stearate
	100.00	

immune response of tilapia, but they have also enhanced disease resistance against *S. iniae* (Gültepe et al. 2014). A methanolic extract of black cumin has stimulated some innate humoral immune responses in rainbow trout (Altunoglu et al. 2017). An extract of caper (*Capparis spinosa*) has been shown to stimulate innate immunity and enhance the growth performance of rainbow trout (Bilen et al. 2016b). A methanolic extract of tetra (*Cotinus coggygria*) has provided resistance in cultured koi carp (*Cyprinus carpio* L.) against *Vibrio anguillarum* infection (Bilen et al. 2013). A recent study has revealed that a 0.3% supplementation of fumitory extract increased growth performance and antioxidant status in rainbow trout (Filogh et al. 2023). An aqueous methanolic extract of celery has proven efficient not only in improving growth but also in enhancing immunity to and resistance against *V. anguillarum* infection (Güroy et al. 2022).

The medicinal plant used in the present study showed antibacterial activity against the fish pathogens tested. Previous studies indicated that *V. arctostaphylos* L. exhibits antibacterial activity (Mohammadi-Aloucheh et al. 2018, Bayrami et al. 2019, Khodadadi et al. 2021). Specifically, the essential oil of *V. arctostaphylos* using MIC revealed antibacterial activities against most of the bacteria tested, including *Escherichia coli*, *Klebsiella pneumoniae*, *Streptococcus pneumonia*, and *Enterococcus faecalis* (Teimouri 2015). Aqueous methanol extracts of *V. arctostaphylos* fruit showed sensitivity to *Salmonella* and *E. coli* species at MIC values of 50–200 mg mL^{-1}

Table 2
MIC values of the aqueous methanolic extract of cultivated Caucasian whortleberry (*Vaccinium arctostaphylos* L.)

	Fish pathogens					
Concentration (mg mL^{-1})	*Yersinia ruckeri*	*Pseudomonas putida*	*P. luteola*	*Aeromonas salmonicida*	*A. hydrophila*	*A. sobria*
140	-	-	-	-	-	-
70	-	-	-	-	-	-
35	-	-	-	-	-	-
17.50	-	-	-	-	-	-
8.75	-	-	-	-	-	-
4.38	+	+	+	+	+	-
2.19	+	+	+	+	+	-
1.09	+	+	+	+	+	+
0.55	+	+	+	+	+	+
0.27	+	+	+	+	+	+
0.14	+	+	+	+	+	+
0.07	+	+	+	+	+	+

(Moeini et al. 2015, 2016). A related species of a the medicinal plant tested, *Vaccinium vitis-idaea* L., also showed a strong antibacterial effect against *Pseudomonas aeruginosa* and *Pseudomonas fluorescens* (Laslo and Köbölkuti 2017).

The major compound in our extract, 4,8,13-Cyclotetradecatriene-1,3-diol,1,5,9-trimethyl-12-(1-methylethyl)-, was also one of the dominant compounds with bactericidal and antioxidant potential produced by the endophytic fungus *Alternaria alternate* AE1 that was isolated from the medicinal plant *Azadirachta indica* A. Juss (Chatterjee et al. 2019). The second dominant compound in the extract of *V. arctostaphylos* L., 3.alpha.,5.alpha.-Cyclo-ergosta--7,9(11),22t-triene-6.beta.-ol, might also have antibacterial ability since, in a previous study, a similar compound, ergosta-4,6,8(14),22-tetraen-3-one, that was obtained from endophytes isolated from the medicinal plant *Ampelopsis grossedentata* demonstrated antibacterial potential (Li et al. 2021). 22,23-Dibromostigmasterol acetate was likewise found in oils of *Actinodaphne macrophylla* leaves, a medicinal plant showing antimicrobial potential (Putri et al. 2018). 7,10-Dihydroxy-8(E)-octadecenoic acid, a similar compound to 9-Octadecenethioic acid, 12-hydroxy-, S-t-butyl ester obtained in the present study has been reported to have powerful antibacterial activities (Sohn et al. 2013). Dodecane, which is also a major component of the floral essential oil of *Halimodendron halodendron* has both antibacterial and antioxidant activities (Wang et al. 2011). Moreover, phenol is one of the 32 components in Caucasian whortleberry extract, and, according to the literature, phenolic compounds exhibit antibacterial activity (Bouarab-Chibane et al. 2019). Previous reports have linked the antibacterial activity of *V. arctostaphylos* L. to the presence of proanthocyanidin and anthocyanidin compounds, which have the ability to inhibit the multiplication of bacteria (Hasanloo et al. 2019, Khodadadi et al. 2021). However, some studies suggest that, instead of a single compound, the synergistic or antagonistic effects of multiple compounds in a plant extract could be decisive in its potency (Liu 2003; Taştan and Salem 2021). Therefore, it would be imprudent to link any compound to observed effects without testing each compound separately, which means that which compound(s) responsible for the antimicrobial activity observed in the present study remains unclear.

Conclusion

In conclusion, this study highlights the potential use of the cultivated medicinal plant *V. arctostaphylos* L. against all the fish pathogens tested thanks to the presence of bioactive compounds that have antibacterial activity and that might act individually or synergistically. However, to assess the usefulness of this plant, further in vivo studies should be carried out.

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