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Phytochemicals, Antioxidant Activity, and Biological Activities of *Rosa persica* Root

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Abstract

The present study assessed the phytochemicals and biological activities of *Rosa persica* root extracts. The phytoconstituents of *R. persica* root were quantified by gas chromatography-mass spectrometry (GC-MS) and ultra-performance liquid chromatography-electrospray ionization-photodiode array detection-mass spectrometry (UPLC-ESI-PDA-MS^n). Concentrations of total phenolic content (TPC), total flavonoid content (TFC), total proanthocyanidin content (TPAC), and antioxidant capacity were also measured in aqueous and ethanol (EtOH) extracts. Their bioactivities in terms of antiviral (against two cell lines), antimicrobial (against eight bacteria strains), antifungal (against two fungal strains), and cytotoxic (against eight cell lines) effects were assessed. The maximum effects were found in EtOH extract of *R. persica* root. The main components of the *R. persica* essential oil (RPEO) were methyl eugenol (73.1%) and geranyl acetone (10.3%). UPLC–ESI-PDA–MSn analysis showed that gallic acid (GA) was found in the highest concentration in the EtOH extract (461.80 ± 90.3 µg/g). In the antiviral assay, the half maximal inhibitory concentrations (IC_{50}) of EtOH extract for *Coxsackievirus B3* (*CV-B3*) and *Coxsackievirus B4* (*CV-B4*) were 29.26 ± 0.5 and 24.70 ± 0.2 µg/mL, respectively. The cytotoxic concentrations (CC_{50}) calculated for EtOH extract against both cell lines were significantly lower than aqueous extract (89.13 ± 0.3 and 75.03 ± 0.1 µg/mL, respectively). The most sensitive bacteria strain in both extracts was *Staphylococcus aureus.* Activity in fungal strains, *Candida albicans* was more sensitive than *Aspergillus niger*. The current cytotoxicity results between the two extracts of *R. persica* showed that both had the highest and lowest cytotoxic activity against human glioblastoma (U-87-MG) and human breast cancer (MDA-MB-231) cell lines, respectively.

Keywords Anticancer · Antimicrobial · Bioactive compounds · *Coxsackieviruses* · Phytochemicals

Introduction

Iran is one of the top ten countries that introduced 1727 endemic species of 8000 species of plants. The genus *Rosa* belongs to the rose family with about 100 species (Korkmaz and Dogan 2018; Sadat-Hosseini et al. 2017). These species are commonly used in the food industry (juice, jam, and herbal tea) and traditionally to treat cold and flu, infectious, and inflammatory conditions (diabetes, arthritis, and rheumatism) (Tahirović and Bašić 2017). *Rosa persica*, known as 'Varak,' is native to Iran, Afghanistan, Central Asia, and north of western Siberia. With a distinctive red eye in the center of the yellow petals, *R. persica* is a dwarf perennial shrub (Basaki et al. 2009). The plant protection system against insects, microorganisms, and the sun's rays are phenolic compounds present in thorny stems (Amini et al. 2016).

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R. persica is widespread in 128 genetically diverse populations due to short-distance seed dispersal and eco-geographic microscale. This species often grows as a weed in fields as well as fuel. It grows best in dry regions on more alkaline soils (Basaki et al. 2009). The flowers, fruits, leaves, and roots of wild rose have been used in traditional medicine. People used the flowers for mild inflammation of the skin or mucous membranes in the mouth and throat. The fruits were used as herbal tea, syrup, and wine. Rose hips have been used primarily for immunosuppressive, anti-inflammatory, analgesic, anti-diabetic, cardioprotective, gastric protective, and skin ameliorative effects (Koczka et al. 2018). From the perspective of Iranian traditional medicine, *R. persica* exerts anti-inflammatory and antimicrobial properties and has been used to treat diarrhea (Ghavi and Mazandarani 2017). A study on traditional Iranian medicine showed the inhibitory effect of *R. persica* on the contraction of the ileum. In this regard, the pharmacodynamic studies also showed that hydroalcoholic and hexane extracts of *R. persica* inhibited the effects on the isolated ileum of rats in a dependent manner due to membrane depolarization, muscarinic receptor or neuronal stimulation, and suggesting broader mechanisms of action. When the myosin light chain is phosphorylated, the smooth muscle contractile machinery is stimulated. Initiation of the enzyme myosin light chain kinase (MLCK) caused the phosphorylation process. The interaction between intracellular Ca2+ ion and calmodulin activated the enzyme (MLCK). Thus, if the extract can affect the final cell contraction pathway, its inhibitory effect will be demonstrated. The next possibility is that several active substances with different mechanisms can produce the inhibitory effect of KCl with plant extract in a concentration-dependent manner. Modern medicine has also shown that *R. persica* extract is more effective compared to other varieties of roses and is also useful in gastrointestinal disorders accompanied by intestinal cramps or diarrhea (Sadraei et al. 2016). *R. persica* has been reported to show antioxidant activity, since it is considered to be a rich source of phenolic compounds, which have been determined by reverse-phase high-performance liquid chromatography (RP-HPLC) (YASA et al. 2009). Studies on *R. persica* essential oil (RPEO) revealed that aliphatic hydrocarbons (heptacosane and nanocosane) are the main components (Amini et al. 2016).

Determining the most efficient solvent for extraction and evaluating its biochemical and biological properties has always been difficult (Taghizadeh et al. 2018). The phenolic compounds with their free radical scavenging activities are known to have antioxidant potential by inducing antioxidant enzyme levels (Alcântara et al. 2019). Limited information is available to quantify individual bioactive compounds in *R. persica*. In general, total phenolic content (TPC) is often estimated by spectrophotometer measurements. However, the spectrophotometric assays have some limits such as the lack of separation process and accurate quantitative results of individual phenols. It is recommended to estimate the phenolic compounds with both the Folin–Ciocalteu and ultra-performance liquid chromatography-electrospray ionization-photodiode array detection-mass spectrometry (UPLC–ESI-PDA–MSn) methods. In fact, it is a powerful

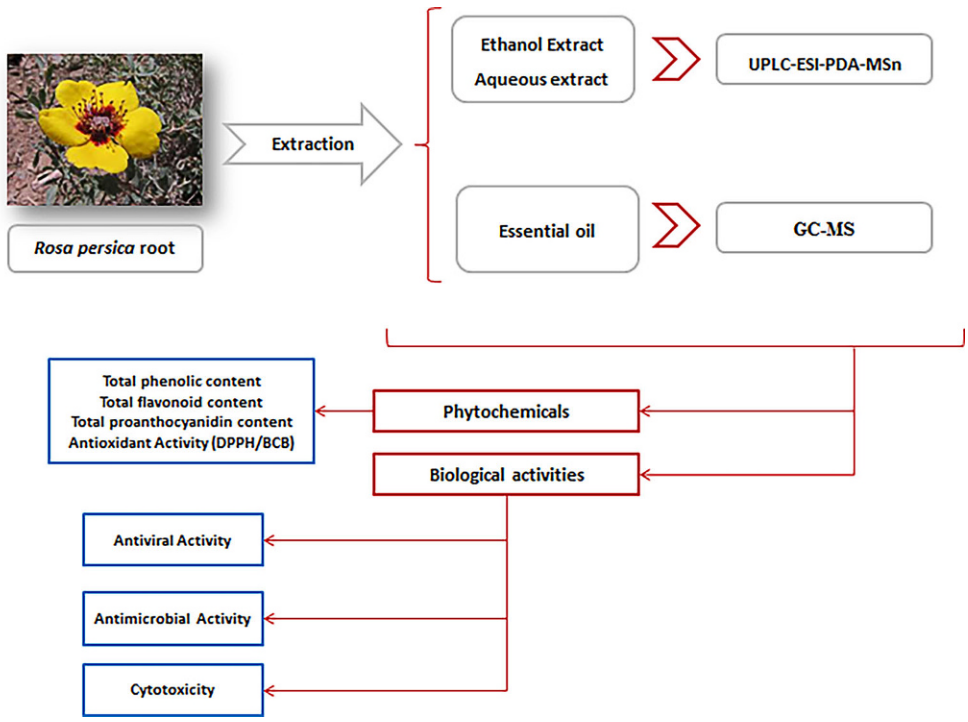

Fig. 1 Schematic presentation of the current study methodology

technique to achieve more knowledge on the metabolite profile of food plants and to link their phytochemicals with health benefits. The current study was conducted to define (I) the TPC, total flavonoid content (TFC), and total proanthocyanidin content (TPAC), (II) the antioxidant capacity, antiviral, antimicrobial, and cytotoxic effects, (III) the phytochemical profile of the RPEO by gas chromatography-mass spectrometry (GC-MS), and (IV) UPLC–ESI-PDA–MSn of the extracts of *R. persica* root (Fig. 1).

Materials and Methods

Reagents and Standards

Folin–Ciocalteu's reagent (CAS: 7732-18-5), gallic acid (GA) (CAS: 149-91-7), quercetin (QE) (CAS: 117-39-5), potassium acetate (CAS: 127-08-2), aluminum (III) chloride (CAS: 7446-70-0), sodium bicarbonate (SB) (CAS: 144-55-8), and 2, 2'-diphenyl 1-picrylhydrazyl (DPPH) (CAS: 1898-66-4) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Milli-Q water (CAS: 7732-18-5) and acetonitrile (CAS: 75-05-8) (UPLC-MS grade) was purchased from Merck. Roswell Park Memorial Institute (RPMI), fetal bovine serum (FBS) (CAS: 9014-81-7), phosphate buffered saline (PBS) (CAS: 7647-14-5), trypsin-EDTA solution (170,000 U/L trypsin and 0.2 g/L EDTA) (CAS: 9002-07-7), and penicillin/streptomycin solution (10,000 U/mL penicillin and 10 mg/mL streptomycin) (CAS: 113-98-4) were obtained from Gibco. AlamarBlue® (resazurin) (CAS: 153796-08-8) was purchased from Sigma (Saint Louis, MO, USA). All the chemicals were of analytical grade.

Plant Materials

The roots of *R. persica* were collected in Shirvan, North Khorasan Province, Iran at 3732 N and 5754 E at 1093 meters above sea level. The average minimum and maximum temperatures of the corresponding zone were –1.1 and 25.8 °C, respectively, and the total precipitation was 279 mm (Mashhad Meteorological Organization, Iran).

Extraction Methods and Extract Preparation

The root of *R. persica* was washed with distilled water, air-dried at room temperature (18 °C; dark place) for 5 days, and then stored at 4 °C until use. Dried materials were grounded; 50 g of sample was extracted with ethanol (EtOH) (98% purity) and distilled water for 48 h at room temperature. The extract was filtered by using Whatman® No. 1. The solvents were evaporated under reduced pressure to afford several extracts; both extracts were then stored at –80 °C (Taghizadeh et al. 2019b).

Essential Oil (EO) Preparation

The dried roots were chopped and crushed in a mortar and pestle. Crushed roots were subjected to hydrodistillation using the Clevenger apparatus. Then, 100 g of the root was added to 800 ml of distilled water. It was placed in a balloon heater connected to a refrigerator for 3 h to ensure condensation of EO. At the end of EO extraction, both the aqueous phase and the EO phase were observed. The RPEO was dried over anhydrous sodium sulfate and stored in the sealed vials at –20 °C until use. Experiments were performed twice for each condition (Azadmanesh et al. 2021).

Extraction Yield (Content)

The extraction yield of the RPEO was calculated using Eq. 1:

$$\text{Extraction yield } (\%) = \frac{\text{Volume of essential oil collected } (\mu l)}{\text{Initial weight of the dry plant } (g)} \times 100 \quad (1)$$

Instrumentation Analysis Methods: GC-MS Analysis

The analyses were assessed by GC-MS on PAL RTC 120 sampler (Agilent 7890B series gas chromatograph and Agilent 5977A series MS spectrometer) and well-found with Wiley 7n.Llibrary. The specifications of GC-MS are given in Table 1 (Farhadi et al. 2020; Singh et al. 2022).

UPLC–ESI-PDA–MSn

MS analysis data was obtained from UPLC 1200 series (Agilent Tech—Germany) instrument using column; Gemini 3 mm C18 110 A° from phenomenex with dimensions 100 × 1 mm i.d., protected with RP C18 100 A° guard column with dimensions (5 mm × 300 mm i.d., 5 mm). Mobile phase were prepared of 2% acetic acid (A) and 90% Methanol (MeOH) (B) at flow rate of 0.5 mL/min. The sample injection volume was 10 µL, so that each sample was dissolved in 2% acetic acid and 5% MeOH. A Fourier transform ion cyclotron resonance MS analyzer used equipped with ESI system. In order to control the system, X-calibur® software version 2.1 was used. Detection was performed in the negative ion mode by using a capillary voltage of 36 V in 275 °C. The API source voltage and the de-solvation temperature were regulated on 5 kV and 275 °C, respectively. Nitrogen gas with a flow of 15 mL/min was used as a nebulizing gas. The full MS scan included the MS range from

Table 1 Specification of GC-MS

GC-MS Specifications	Condition
Equilibration time	50 min
Loop temperature	110 °C
Transfer line temperature	130 °C
Shaking time	6 min
Injecting time	0.5 sec
Column	HP-5 MS (30 m × 250 µm I.D., film thickness 0.25 µm)
Carrier gas	Helium (at a flow rate of 1.0 mL/min)
Temperature program	a) 50 °C held for 5 min, raised to 3 °C/min to 140 °C b) 240 °C held for 10 min c) Held isothermally for 10 min
Split ratio	1:10
Total analysis	55 min
MS detection	
Electron ionization	70 eV
Abundance of ions	Full-scan mode from m/z 40 to 500
Ion source temperature	230 °C
Quadrupole temperature	150 °C

150 to 2000 m/z (Chakraborty et al. 2017; Handoussa et al. 2013).

Phytochemical Content

TPC

Briefly, 20 µL of the extract was mixed with 100 µL Folin–Ciocalteau reagent and diluted 10 times in distilled water. Then, 1.5 mL distilled water was added to the solution and stored at room temperature for 5 min. A total of 300 µL SB (20% w/v) was added and the mixture was incubated in a dark place for 2 h. The absorbance of each sample was read using a UV-visible spectrophotometer (Cecil, UK) at 725 nm. A calibration curve was constructed by standard solution of GA (0.2–1 mg/mL) (Trandafir and Cosmulescu 2020). Results were expressed as mg GA/g dried extract (DE) (mg GA/g DE) (Fattahi et al. 2021).

TFC

For TFC assay, 0.5 mL of DE was mixed with 0.1 mL aluminum chloride (10%), 1.5 mL EtOH (95%), 0.1 mL potassium acetate (1 M), and 2.8 mL distilled water. After incubating the extract at room temperature for 30 min, the absorbance was read at 415 nm. The sample contained 5 mL extract solution and 5 mL MeOH without $AlCl_3$. The TFC was presented as milligram of QE per gram of DE (mg QE/g DE) (Naik and Al-Khayri 2020).

TPAC

Quantitative estimation of TPAC was assessed by the vanillin-HCl method. Then, 0.5 ml was mixed with 1.5 mL 4% vanillin methanol solutions and 0.75 mL M HCl. After 20 min incubation at 30 °C, the absorbance was read at 500 nm. Based on calibration curve, TPAC was reported as milligram of catechin/g DE (Boso et al. 2019).

In Vitro Antioxidant Assays

DPPH Assay

In order to determine radical scavenging ability, 50 µL of different concentrations of the extract was added to the same value of MeOH DPPH solution (0.1 mM). The mixture was incubated at 30 °C for 20 min while being shaken. The absorbance of the samples was read at 517 nm (Zor et al. 2022). The antioxidant activity was calculated as percent inhibition by following Eq. 2 (Kamble et al. 2020):

$$\text{Inhibition of DPPH activity } (\%) = \frac{\text{BA} - \text{SA}}{\text{BA}} \times 100 \qquad (2)$$

BA Blank absorbance
SA Sample absorbance

A curve of percentage of inhibition was plotted against the concentrations of samples; then, the half maximal inhibitory concentration (IC_{50}) was determined. Butylated hydroxytoluene (BHT) was used as a positive control (Xu et al. 2018).

β-Carotene Bleaching (BCB) Assay

For this assay, 20 mg linoleic acid was mixed with 100 mg Tween 40 and 1 mL β-carotene solution (0.2 mg/mL in chloroform). After chloroform was evaporated at 50 °C, 100 mL distilled water was mixed and emulsified by sonication for 1 min (emulsion A). Following, 20 mg linoleic acid was mixed with Tween 40 (200 mg) and oxygenated water (50 mL) (emulsion B). Then, 200 µL of each concentration of DE and BHT (as positive control) were added with emulsion A (5 mL). Also, a control was provided by mixing 200 mL MeOH with 5 mL of emulsion A. A mixture of 200 µL MeOH and 5 mL of emulsion B was used for calibration. The absorbance was read at 470 nm before and

after 120 min of incubation. The inhibition percentage was calculated using Eq. 3 (Esmaeilzadeh Kenari et al. 2014):

$$\text{Inhibition percentage (\%)} = \frac{\text{SA at 120 min} - \text{CA at 120 min}}{\text{CA before incubation} - \text{CA at 120 min}} \times 100 \quad (3)$$

CA Control absorbance
SA Sample absorbance

Biological Assays

Antiviral Assay

Cell Culture The antiviral activity was estimated on the *CVB3* and *CVB4* cells. The cells were incubated in eagle's minimal essential medium supplemented with 10% heat inactivated fetal calf serum (FCS, Gibco BRL), 1% (2 mM) L-Glutamine, 1% (50 µg/mL) streptomycin, 1% (50 IU/mL), penicillin, 1% non-essential amino acids and 1% (2.5 µg/mL) Fungizone (Amphoterin B, Apothecon). The virus titer was identified as $TCID_{50}$ (the 50% tissue culture infection dose) on human epithelial cell line 2 (HEp-2) and stored at –80 °C (Gore and Desai 2014; Taghizadeh et al. 2021a).

Cell Viability Assay

Briefly, HEp-2 cells were plated at a density of 10^4 cells/well and cells into 96 well plates in a humidified atmosphere at 37 °C in 5% CO_2. After 30 h, the medium culture was removed, cells were washed with phosphate-buffered saline (PBS). Then, 100 µL of each extract were diluted in minimum essential medium (MEM) 2% FCS. Cells were injected with 50 µL of 2% MEM (including 100 $TCID_{50}$ of *CVB-3* and *CVB-4*). The probable cytopathic effect was controlled daily. The percentage of viability was determined using the Eq. 4 and the selectivity index (SI) was calculated through Eq. 5 (Taghizadeh et al. 2020):

$$\text{Inhibition of vius inhibition (\%)} = \frac{\text{OD of treated cells} - \text{OD of virus control}}{\text{OD of cell control} - \text{OD of virus control}} \times 100 \quad (4)$$

OD Optical density

$$SI = \frac{CC50}{IC50} \quad (5)$$

CC_{50} The cytotoxic concentrations
SI Selectivity index
IC_{50} Half maximal inhibitory concentrations

Antimicrobial Assay

Culture Media Preparation and Bacterial Strains The antimicrobial effects of the extracts were assessed against four Gram-negative bacterial strains including *Salmonella typhi, Escherichia coli, Pseudomonas aeruginosa*, and *Serratia marcescens*, as well as four Gram-positive including *Staphylococcus aureus, Bacillus cereus, Micrococcus luteus,* and *Staphylococcus epidermidis*. All the strains were seeded for 24 h at 37 °C on soybean casein digest agar (SCDA) and adjusted to 10^6 CFU/mL with sterile normal saline (NS) (0.9%) (Majiya and Galstyan 2020).

Minimum Bactericidal Concentration (MBC) and Minimum Inhibitory Concentration (MIC)

The extracts were melted in Muller Hinton broth (MHB) by dimethyl sulfoxide (DMSO). The concentration (10% v/v) was set by adding each extract (650 µL) to DMSO (320 µL) and MHB. The volume was finally adjusted to 6.5 mL. According to the serial dilution method, 200 µL of each level was inoculated in each cell culture plate. Then, 20 µL of bacterial suspension (10^6 CFU/ml) was added. The tests were also inoculated separately in the culture media as positive control (gentamicin and vancomycin). Moreover, MHB was used as negative control. The samples were kept at 37 °C for 24 h, then the bacterial growth of each well was measured by adding 20 µL of 2, 3, 5-triphenyltetrazolium chloride (TTC) (5 mg/mL) as a colorimetric indicator. They were incubated again at 37 °C for 1 h. The MIC value was calculated based on the lowest concentration of the extract inhibiting the main color of the culture media to red. The MBC value was also identified by content of wells not yielding any red color (24 h, 37 °C). All experiments were done in triplicate (Aziman et al. 2014).

Antifungal Assay

The antifungal assay was examined against *Candida albicans* and *Aspergillus niger*. After culture on SCDA (48 h, 25 °C), sterile 0.9% NS was used to prepare a suspension of 10^6 CFU/mL. The volume of extracts was adjusted to 1 mL by Sabouraud's dextrose broth (SDB). The other concentrations of extracts were made with serial dilution technique. A total of 200 µL of cell suspension was incubated (48 h, 25 °C), and then the MIC and the minimum fungicidal concentration (MFC) values were also considered. The

SDB (positive) and nystatin (negative) were used as controls (Taghizadeh et al. 2019a).

Cytotoxic Assay

Determination of Cell Viability MCF-7 (human breast cancer), DU-145 (human prostate cancer), PC3 (human prostate cancer), A2780 (ovarian carcinoma), C-26 (colorectal cancer), U-87-MG (human glioblastoma), MDA-MB-231 (human breast cancer), Hela, and NIH 3T3 (mouse embryonic fibroblast) were purchased from the Pasteur Institute, Tehran, Iran. These cells were preserved by 10% (v/v) FBS (Gibco, BRL), penicillin/streptomycin (100 IU/mL), and L-glutamine (2 mM). Cultures were incubated at 37 °C under CO_2/air (5%/95%) (Shakeri et al. 2019).

Measurement of Cytotoxic Activity of the Plant Extracts by AlamarBlue®

Cytotoxicity was assessed using AlamarBlue® proliferation assay. Cells were plated on 96-well microplates at a density of 1×10^4. After 24 h, the cells were treated with the different concentrations of extracts (50–400 µg/mL). After 48 h treatment, the cells were treated with 20 µL of AlamarBlue® reagent. After 2–4 h the absorbance was measured at 600 nm. Doxorubicin (Dox) was used as a positive control (Taghizadeh et al. 2021b).

Statistical Analysis

Statistical analysis was presented as mean ± SD. One way ANOVA and LSD test were used to determine statistical differences among groups by JMP 8 (SAS Campus Drive, Cary) (P <0.05 and n = 3).

Results

RPEO Yield and Components

Based on our findings, the ethanol and aqueous extracts were 97.11 and 79.85%, respectively (Table 4). In RPEO, the major components were methyl eugenol (73.1%) and geranyl acetone (10.3%). GC-MS analysis of RPEO chemical composition exposed 35 components in RPEO accounting for 98.4% (Table 2).

UPLC–ESI-PDA–MSn Analysis of Metabolic Extracts

A total of 32 compounds were identified in *R. persica* root extracts, as shown in Table 3. Based on the deprotonated molecular ions, the concentration of phenolic acids was significant differed between the solvents. The compounds GA (461.80 ± 90.30 µg/g), chlorogenic acid (302.50 ± 21.23 µg/g), and quinic acid (250.11 ± 61.70 µg/g) were found in highest concentrations in EtOH extract (Table 3).

Table 2 Chemical components of *R. persica* essential oil (RPEO)

No	Compounds	Concentration (%) RPEO	RT	KI
1	α-Pinene	4.3	7.2	934
2	Camphene	0.1	7.5	950
3	Mintsulfide	0.1	7.3	971
4	Myrcene	0.1	8.0	985
5	β-Pinene	0.1	8.2	990
6	α-Phellandrene	0.1	8.3	1001
7	ρ-Pymene	0.1	9.0	1020
8	Limonene	0.1	9.0	1025
9	**Methyl eugenol**	**73.1**	9.5	1029
10	γ-Terpinene	0.1	9.2	1055
11	Terpinolene	0.1	9.3	1083
12	Diisobutyl phthalate	tr	10.1	1098
13	Endo-Fenchol	tr	10.2	1113
14	**Geranyl acetone**	**10.3**	10.5	1120
15	5E,9E-Farnesyl acetone	0.1	10.0	1135
16	*Cis*-Vebenole	0.5	10.5	1140
17	Elemicin	0.1	12.2	1158
18	1,8-Cineol	6.1	11.3	1165
19	Terpinen-4-ol	0.1	11.2	1173
20	Cryptone	0.1	11.5	1180
21	α-Terpineol	0.1	11.3	1188
22	Myrtenal	0.1	11.4	1198
23	Cuminaldehyde	0.1	11.5	1233
24	α-guaiene	0.1	12.5	1437
25	Allo-aromadendrene	0.1	12.4	1459
26	Bicyclogermacrene	tr	13.3	1493
27	*Cis*-Phytol	1.0	13.4	1530
28	α-Longipinanol	0.1	14.5	1568
29	Spathulenol	tr	14.1	1575
30	E-Nerolidol	tr	14.3	1580
31	1,10-di-epi-Cubenol	0.1	15.3	1588
32	Longiborneol	0.1	15.4	1598
33	γ-Eudesmol	0.1	15.5	1633
34	β-Eudesmol	0.5	16.1	1650
35	α-Eudesmol	0.4	16.2	1658
–	Total	98.4	–	–

The compounds that were highlighted showed higher concentration. *KI* Kovats index, *RPEO R. persica* essential oil, *RT* retention time, *tr* Trace (≤0.05%)

Table 3 Metabolites identified in *R. persica* root extracts by ultra-performance liquid chromatography-electrospray ionization-photodiode array detection-mass spectrometry (UPLC–ESI-PDA–MSn)

No	Compound	Ethanol extract (means ± SD in μg/g)	Aqueous extract (means ± SD in μg/g)	Molecular formula	Molecular weight (M)	UPLC–ESI-PDA–MSn (m/z)	
						RT (min)	$(M-H)^{-1}$
1	Succinic acid	15.41 ± 1.30^{fg}	3.85 ± 0.50^{g}	$C_4H_6O_4$	118.08	0.9	116.532
2	Pyrogallol	1.05 ± 0.10^{g}	6.01 ± 0.10^{g}	$C_6H_6O_3$	126.11	1.0	125.051
3	Malic acid	112.12 ± 23.5^{d}	67.32 ± 11.5^{e}	$C_4H_6O_5$	134.08	1.1	133.131
4	Citric acid	88.45 ± 20.10^{e}	19.95 ± 10.05^{fg}	$C_6H_8O_7$	192.12	1.2	191.011
5	Gallic acid	461.80 ± 90.30^{a}	177.80 ± 90.30^{d}	$C_7H_6O_5$	170.12	1.3	168.411
6	Quinic acid	250.11 ± 61.70^{c}	94.21 ± 13.20^{e}	$C_7H_{12}O_6$	192.17	1.8	191.121
7	4-Hydroxybenzoic acid	22.55 ± 3.14^{efg}	9.15 ± 1.10^{fg}	$C_7H_6O_3$	138.12	1.9	137.211
8	3-4-Hydroxybenzoic acid	13.02 ± 1.11^{fg}	2.73 ± 0.55^{g}	$C_7H_6O_4$	154.12	2.0	153.101
9	Chlorogenic acid	302.50 ± 21.23^{b}	100.45 ± 9.64^{d}	$C_{16}H_{18}O_9$	354.31	2.3	353.103
10	Caffeoyl Quinic acid	122.83 ± 31.40^{d}	76.80 ± 27.04^{e}	$C_{16}H_{17}O_9$	354.31	2.5	353.052
11	Esculetin	30.14 ± 6.03^{ef}	18.93 ± 1.32^{fg}	$C_9H_6O_4$	178.14	3.0	177.104
12	Vanillic acid	9.71 ± 1.20^{fg}	3.01 ± 0.70^{g}	$C_8H_8O_4$	168.14	3.1	167.011
13	Caffeic acid	125.15 ± 10.40^{d}	66.24 ± 9.53^{e}	$C_9H_8O_4$	180.16	3.1	178.512
14	Syringic acid	111.73 ± 19.04^{d}	98.20 ± 6.15^{e}	$C_9H_{10}O_5$	198.17	3.1	197.045
15	Catechin	35.11 ± 2.00^{ef}	11.80 ± 1.91^{fg}	$C_{15}H_{14}O_6$	290.27	3.2	289.064
16	Caffeic acid 3-glucoside	98.53 ± 12.00^{e}	61.22 ± 10.02^{e}	$C_{15}H_{18}O_9$	342.30	4.2	341.021
17	Sinapic acid	28.33 ± 5.01^{efg}	15.52 ± 3.12^{fg}	$C_{11}H_{12}O_5$	224.21	4.8	223.012
18	Ferulic acid	42.12 ± 2.12^{ef}	20.33 ± 2.40^{efg}	$C_{10}H_{10}O_4$	194.18	5.0	193.012
19	Tannic acid	95.75 ± 3.45^{e}	32.61 ± 4.11^{efg}	$C_{76}H_{52}O_{46}$	1701.20	5.4	1700.012
20	Naringin	82.75 ± 3.45^{e}	51.01 ± 2.70^{e}	$C_{27}H_{32}O_{14}$	580.54	5.5	579.154
21	Benzoic acid	67.13 ± 5.12^{e}	21.44 ± 3.14^{efg}	$C_7H_6O_2$	122.12	5.9	121.031
22	4-Hydroxycoumarin	21.00 ± 2.10^{efg}	6.30 ± 0.80^{fg}	$C_9H_6O_3$	164.16	6.1	163.132
23	Hesperidin	43.73 ± 5.03^{ef}	15.60 ± 2.41^{fg}	$C_{28}H_{34}O_{15}$	610.56	6.2	609.172
24	8-Epiloganic acid	33.02 ± 2.01^{ef}	9.23 ± 1.00^{fg}	$C_{16}H_{24}O_{10}$	376.36	6.4	375.013
25	Rosmarinic acid	88.51 ± 4.22^{e}	18.64 ± 2.00^{fg}	$C_{18}H_{16}O_8$	360.31	6.9	359.121
26	Vicenin	21.11 ± 1.72^{efg}	11.04 ± 1.75^{fg}	$C_{27}H_{30}O_{15}$	594.50	7.3	593.112
27	Resveratrol	21.40 ± 1.90^{efg}	70.83 ± 2.10^{e}	$C_{14}H_{12}O_3$	228.24	8.2	227.011
28	Isorhamnetin-3-O-rutinoside	35.85 ± 1.41^{ef}	10.02 ± 2.51^{fg}	$C_{28}H_{32}O_{16}$	770.70	10.5	769.013
29	Methylhypolaetin-acetyl-allosyl-hexoside	61.33 ± 3.25^{e}	29.52 ± 4.10^{efg}	$C_{30}H_{33}O_{18}$	681.16	19.4	680.010
30	Methylhypolaetin-acetyl-allosyl-hexoside-isomer	54.10 ± 2.31^{e}	23.15 ± 1.72^{efg}	$C_{30}H_{33}O_{18}$	681.16	21.3	680.012
31	Anisofolin A	9.32 ± 0.90^{fg}	2.13 ± 0.50^{fg}	$C_{39}H_{32}O_{14}$	724.70	22.1	723.011
32	Rosmarinic Acid Methyl Ester	65.43 ± 2.31^{e}	41.13 ± 3.04^{ef}	$C_{19}H_{18}O_8$	374.30	28.5	373.014

Lowercase superscripts (a, b, c, etc.) express statistical variations among different solvents. The values with at least one similar superscript are not significantly different from each other, but those with different superscripts are significantly different
RT retention time, *SD* standard deviation

Table 4 TPC, TFC, TPAC, and antioxidant activity of *R. persica* root extracts (means ± SD)

Solvent	Extraction yield (%)	TPC	TFC	TPAC	DPPH (IC_{50})	BCB (IC_{50})
Water	79.85 ± 2.5^{b}	53.05 ± 1.7^{b}	46.11 ± 1.0^{b}	49.15 ± 1.1^{b}	86.00 ± 1.5^{a}	93.44 ± 2.1^{a}
EtOH	97.11 ± 2.3^{a}	98.73 ± 2.5^{a}	85.33 ± 2.2^{a}	90.05 ± 2.3^{a}	19.22 ± 0.8^{bcd}	46.02 ± 1.2^{bc}
BHT	–	–	–	–	6.41 ± 0.3^{e}	23.03 ± 1.3^{d}

In each column, lowercase superscripts (a, b, c, etc.) express statistical variations among different solvents. The values with at least one similar superscript are not significantly different from each other but those with different superscripts are significantly different
BCB β-carotene linoleic acid bleaching, *BHT* butylated hydroxytoluene, *DPPH* DPPH radical scavenging activity (IC_{50}; μg/mL), *SD* standard deviation, *TFC* total flavonoid content (mg quercetin per g dried extract), *TPAC* proanthocyanidin content (mg catechin per g dried extract), *TPC* total phenolic content (mg gallic acid per g dried extract)

Phytochemical Content and Antioxidant Activity

Table 4 revealed that the use of EtOH resulted in extraction of higher TPC, TFC, and TPAC from *R. persica* root (Table 4). The content of TPC varied from 53.05 ± 1.7 mg GA/g DE in aqueous extract to 98.73 ± 2.5 mg GA/g DE in EtOH extracts. The EtOH extracts of *R. persica* root had the highest contents of TFC (85.33 ± 2.2 mg of QE/g DE) and TPAC (90.05 ± 2.3 mg of catechin/g DE). As can be seen, among the *R. persica* root extracts in the DPPH assay, the EtOH extract exhibited the IC_{50} value of 19.22 ± 0.8 µg/mL, which is weaker than BHT (IC_{50} = 6.41 ± 0.3 µg/mL). Results of the BCB assay were also expressed as IC_{50}. The IC_{50} values of *R. persica* root extracts in the BCB assay were in the range 46.02 ± 1.2 µg/mL to 93.44 ± 2.1 µg/mL. The EtOH extract showed the highest percentage of BCB inhibition. It was interesting to note that a high correlation was detected between phenolic compounds and antioxidant activities in both antioxidant assays (Table 4).

Biological Effects

Antiviral Effects

The antiviral activity of *R. persica* root extracts was evaluated against *Coxsackievirus B3* (*CV-B3*) and *Coxsackievirus B4* (*CV-B4*). To evaluate the potential use of *R. persica* root extracts, we tested the inhibition of virus-induced pathogenicity on HEp-2 cells. The mean IC_{50}, CC_{50}, and SI values for each extract are shown in Table 5. The IC_{50} values of *R. persica* EtOH extracts for *CV-B3* and *CV-B4* were 29.26 ± 0.5 and 24.70 ± 0.2 µg/ml, respectively. Higher IC_{50} values indicate the lowest percentage of inhibition. The aqueous extracts were less potent (106.05 ± 0.3 and 86.10 ± 0.2 µg/mL). Based on our results, CC_{50} values calculated for EtOH extract against both *CV-B3* and *CV-B4* cell lines were significantly less than these values of the aqueous extract (89.13 ± 0.3 and 75.03 ± 0.1 µg/mL, respectively). The SI of various extracts for both cell lines were above 3.

Antimicrobial Effects

As shown in Table 6, *S. aureus* was the most sensitive strain in both extracts. The aqueous and EtOH extracts had different MIC values against *S. aureus* (20.20 and 7.00 µg/mL, respectively). Moreover, the MBC values against relevant bacteria were reported in aqueous and EtOH extracts (25.90 and 10.00 µg/mL, respectively). Moreover, in fungal strains, *C. albicans* was more sensitive than *A. niger*. The MIC and MFC values against *C. albicans* for aqueous and EtOH extracts were 55.20 and 67.00 µg/mL, as well as 22.00 and 29.00 µg/mL, respectively. Furthermore, the MIC and MFC values for aqueous extract was 81.10 and 90.22 µg/mL against *A. niger*, and these values were 43.00 and 58.00 µg/mL, respectively against *A. niger* with respect to EtOH extract. Both samples presented antifungal and antibacterial efficacy at significantly different levels (Table 6).

Cytotoxicity Effects

After 48 h of treatment, we found that both extracts had the highest cytotoxic activity against U-87-MG. The IC_{50} values were determined for aqueous and EtOH extracts, against U-87-MG were 51.22 ± 3.41 and 10.10 ± 1.02 µg/mL, respectively. The aqueous and EtOH extracts showed the lowest cytotoxic activity against MDA-MB-231cell (IC_{50} = 100.00 ± 4.85 and 80.55 ± 3.23 µg/mL, respectively) (Table 7).

Discussion

The current study evaluated the phytochemicals (e.g., TPC, TFC, TPAC, and phenolic acids), antioxidant capacity, and biological activities of *R. persica* root extracts. Our results showed that the EtOH extract of *R. persica* had significantly different phytochemicals and biological effects. This led us to realize that polar protic solvents such as EtOH are the most efficient. Based on the current results, there were significant differences between water and EtOH used for extraction in terms of TPC, TFC, and TPAC. These results agreed with those reported by Yu et al. (Yu et al.

Table 5 Assessment of antiviral activity of various *R. persica* root extracts

	CV-B3			*CV-B4*		
Solvent	CC_{50}	IC_{50}	SI	CC_{50}	IC_{50}	SI
Water	472.60 ± 1.03^{a}	106.05 ± 0.3^{a}	4.45^{a}	376.70 ± 0.1^{a}	86.10 ± 0.2^{a}	4.37^{a}
EtOH	89.13 ± 0.3^{bc}	29.26 ± 0.5^{bc}	3.04^{ab}	75.03 ± 0.1^{bc}	24.70 ± 0.2^{b}	3.03^{ab}

In each column, lowercase superscripts (a, b, c, etc.) express statistical variations among different solvents. The values with at least one similar superscript are not significantly different from each other, but those with different superscripts are significantly different

CC_{50} cytotoxic concentration required to reduce the number of viable cells by 50% (µg/mL), *CV-B3* Coxsackievirus B3, *CV-B4* Coxsackievirus B4, *IC_{50}* concentration of the sample required for 50% inhibition (µg/mL), *SI* selectivity Index (CC_{50}/IC_{50})

Table 6 MIC, MBC, and MFC (µg/mL) of *R. persica* root extracts

Microorganism	Aqueous extract		EtOH extract		Gentamicin		Vancomycin		Nystatin	
Bacterial strains	**MIC**	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**
S. aureus PTCC 1337	20.20 ± 1.55^{gh}	25.90 ± 1.01^{f}	7.00 ± 0.10^{f}	10.00 ± 0.90^{f}	–	–	2.00 ± 1.55^{b}	54.00 ± 3.25^{a}	–	–
S. epidermis PTCC 1435	25.00 ± 1.65^{g}	26.00 ± 1.42^{f}	10.00 ± 1.00^{f}	15.00 ± 1.05^{ef}	–	–	4.00 ± 1.00^{a}	16.00 ± 1.21^{c}	–	–
B. cereus PTCC 1247	51.00 ± 3.00^{e}	60.00 ± 4.50^{e}	20.00 ± 6.55^{e}	37.55 ± 3.25^{d}	–	–	4.00 ± 1.00^{a}	20.20 ± 1.50^{b}	–	–
M. luteus ATCC 9341	43.10 ± 3.30^{ef}	59.00 ± 3.22^{e}	17.00 ± 5.00^{e}	20.10 ± 2.00^{e}	–	–	2.00 ± 0.80^{b}	20.00 ± 1.73^{b}	–	–
E. coli ATCC 10536	180.10 ± 11.00^{a}	197.00 ± 13.22^{a}	120.0 ± 11.00^{a}	180.00 ± 1.62^{a}	8.00 ± 1.33^{c}	16.00 ± 1.50^{c}	–	–	–	–
P. aeruginosa ATCC 15442	100.04 ± 9.55^{d}	120.00 ± 10.23^{d}	83.54 ± 8.12^{cd}	90.00 ± 3.21^{c}	8.00 ± 1.25^{c}	12.00 ± 1.54^{d}	–	–	–	–
S. typhi PTCC 1609	121.00 ± 10.55^{c}	159.00 ± 13.05^{c}	98.44 ± 8.55^{c}	115.00 ± 13.21^{bc}	15.00 ± 1.80^{b}	22.20 ± 2.00^{b}	–	–	–	–
S. marcescens (ATCC 1435)	155.00 ± 11.55^{b}	173.31 ± 14.00^{b}	109.72 ± 10.00^{b}	124.00 ± 10.00^{b}	18.00 ± 1.50^{a}	34.00 ± 2.41^{a}	–	–	–	–
Fungal strains	**MIC**	**MFC**	**MIC**	**MFC**	**MIC**	**MFC**	**MIC**	**MFC**	**MIC**	**MFC**
C. albicans ATCC 10231	55.20 ± 1.13^{b}	67.00 ± 1.80^{b}	22.00 ± 1.55^{b}	29.00 ± 2.55^{b}	–	–	–	–	4.00 ± 0.90^{b}	4.00 ± 0.91^{b}
A. niger ATCC 16404	81.10 ± 2.00^{a}	90.22 ± 2.30^{a}	43.00 ± 3.00^{a}	58.00 ± 3.14^{a}	–	–	–	–	12.00 ± 1.32^{a}	12.00 ± 1.30^{a}

In each column/row of bacterial and fungal strains, lowercase superscripts (a, b, c, etc.) express statistical variations among different solvents/strains/positive controls. The values with at least one similar superscript are not significantly different from each other, but those with different superscripts are significantly different

MBC minimum bactericidal concentration, *MFC* minimum fungicidal concentration, *MIC* minimum inhibitory concentration

Table 7 Cytotoxic effects (IC_{50} µg/mL) of aqueous and EtOH extracts

Cell line	Aqueous extract	EtOH extract	Dox
MCF-7	56.75 ± 3.50^{c}	19.44 ± 1.12^{g}	1.42 ± 0.05^{j}
A2780	70.35 ± 4.02^{bc}	38.44 ± 1.85^{e}	0.20 ± 0.02^{j}
PC3	90.45 ± 4.40^{ab}	17.05 ± 1.00^{g}	0.20 ± 0.02^{j}
DU-145	79.65 ± 4.10^{b}	14.10 ± 1.13^{gh}	0.32 ± 0.03^{j}
U-87-MG	51.22 ± 3.41^{cd}	10.10 ± 1.02^{hi}	0.30 ± 0.02^{j}
C-26	69.92 ± 0.53^{bc}	18.40 ± 1.11^{g}	0.15 ± 0.02^{j}
Hela	90.37 ± 4.20^{ab}	33.62 ± 2.00^{ef}	0.25 ± 0.03^{j}
MDA-MB-231	100.00 ± 4.85^{a}	80.55 ± 3.23^{b}	0.34 ± 0.04^{j}

Dox doxorubicin, *IC50* concentration of the sample required for 50% inhibition, *MCF-7* (Human breast cancer), *A2780* (Ovarian carcinoma), *PC3* (Human prostate cancer), *DU-145* (Human prostate cancer), *U-87-MG* (human glioblastoma), *C-26* (Colorectal cancer), *MDA-MB-231* (Human breast cancer)

2005). In another experiment performed on *Pistacia vera*, the EtOH extract was more efficient in terms of phenolic compound extraction and antioxidant capacity (Taghizadeh et al. 2018). Our results were also consistent with a previous study showing that EtOH extract had a higher concentration of TFC than aqueous extract (Wang and Helliwell 2001). Li et al. expressed that TPC was up to 10-fold higher in polar extract than non-polar extract (Li et al. 2006). Among the secondary metabolites present in *R. persica*, phenolic acids are considered to be the main group associated with numerous pharmacological properties including antioxidant, antiviral, antimicrobial, and cytotoxic activities. It is evident that phenolic compounds are responsible for antioxidant capacity. Several studies indicate that there is a positive correlation between TPC, TFC, TPAC, and antioxidant capacity of various extracts (Llorent-Martínez et al. 2017; Rocchetti et al. 2019; Sarikurkcu et al. 2019). This correlation is due to the presence of hydrogen donor bands in phenolic compounds (Messi et al. 2016). In addition, the differences in the main components have been related to different raw materials, the type of solvent, and the extraction methods in relevant studies. The major component in the UPLC–ESI-PDA–MSn analysis of *R. persica* root extracts was GA, which is consistent with the results reported by Ambigaipalan et al. (Ambigaipalan et al. 2017). Besides, another study showed that different geographic conditions significantly affect the concentration of polyphenolic compounds in some *Rosa* species (Koczka et al. 2018). Based on the DPPH assay, the *R. persica* root extract was shown to have potential antioxidant capacity and moderately scavenged DPPH radical compared to the positive control. The associated evidence showed that the phenolic compounds of *R. persica* were remarkably higher than those of *R. pimpinellifolia* (Mavi et al. 2004).

Moreover, 35 compounds, representing 98.4% of RPEO, were identified in the present study. The main components were methyl eugenol (73.1%) and geranyl acetone (10.3%), respectively. *R. persica* is a rich source of valuable components and bioactive compounds such as heptacosane, isobutyl phthalate, nonacosane, dibutyl phthalate, pentacosane, hexadecanoic acid, linalool, ethyl linoleolate, hexyl hexoate, and octacosane (Amini et al. 2016).

Our results indicated that EtOH was better than water for extraction of the antiviral compounds from *R. persica* root extracts. This study supports the previous findings that natural compounds with multiple inhibitory activities may provide effective therapeutic approaches to treating several diseases. Various TFCs including apigenin, QE, kaempferol, genistein, and galangin showed antiviral activity against *HSV-1* and *HSV-2* (Kumar and Pandey 2013). It was also demonstrated that flavones and flavonols have a synergistic effect against some viruses. It is believed that the main mechanism of antiviral activity of secondary compounds is mediated by the inhibition of enzymes involved in the virus life cycle (Čulenová et al. 2019).

The present study showed that the most sensitive bacteria strain in both extracts was *S. aureus.* Moreover, in fungal strains, *C. albicans* was more sensitive than *A. niger*. In the previous study, the antimicrobial activity among wild British Columbia roses including *R. woodsii, R. nutkana*, and *R. pisocarpa* was investigated. These three different roses exhibited antimicrobial activity (Yi et al. 2007). Another study showed that the petals of *R. canina* exhibited an antimicrobial effect against *S. aureus* (Shiota et al. 2004).

The current cytotoxicity results between the two extracts of *R. persica* showed that both extracts had the highest and the lowest cytotoxic activity against U-87-MG and MDA-MB-231cell lines, respectively. Several studies reported that the TPC and TFC of *Rosa* species can inhibit hepatotoxicity (Liu et al. 2011; Tao et al. 2016; Zhang et al. 2013). Jassbi et al. found that the hydroalcoholic extract of *R. persica* reduced the oxidative stress and balanced between intracellular antioxidants and free radicals (Jassbi et al. 2003). A study assessing the aerial parts extract of *R. persica* against cadmium-hepatotoxicity found that the serum hepatic enzyme levels decreased and oxidative hepatic damage improved with *R. persica* hydroalcoholic extract (Moradkhani et al. 2020). The inhibitory effects of citronellol (0.8–6.4 µg/mL) and geraniol (0.2–3.2 µg/mL) isolated from *R. damascene* EO was observed on rat ileum contraction (Sadraei et al. 2013).

Conclusion

In this study, UPLC–ESI-PDA–MSn and GC-MS profiling, phytochemical, and biological activities of *R. persica* root extracts were assessed. In RPEO, the major components were methyl eugenol (73.1%) and geranyl acetone

(10.3%). GC-MS analysis of RPEO chemical composition exposed 35 components in RPEO accounting for 98.4%. Moreover, a total of 32 compounds were identified in *R. persica* root extracts. The phenolic acids, GA, chlorogenic acid, and quinic acid occurred in high amounts in EtOH extract. The EtOH extract was found to possess remarkable antioxidant activity in the DPPH and BCB assays. The EtOH extract isolated from *R. persica* root presented considerable effects against biofilm-related infections, *CV-B3* and *CV-B4*, and several cell lines. In terms of antimicrobial and antifungal results, the most sensitive strains were *S. aureus* and *C. albicans*, respectively. As EtOH extract presented considerable effects against biofilm-related infections, and several cell lines, it might be employed as an alternative/complementary treatment after further preclinical and clinical studies. To optimize pharmaceutical applications, it is necessary to identify the EtOH extract *in vivo* assay. Meanwhile, ethanol was an efficient solvent for extraction of polyphenol compounds from *R. persica* root, which is safe for human consumption.

Conflict of interest A. Koohestanian, M. Tatari, M. Samadi Kazemi, A. Asgharzade, and S.F. Taghizadeh declare that they have no competing interests.

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