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## Studies of the in vitro anticancer, antimicrobial and antioxidant potentials of selected Yemeni medicinal plants from the island Soqatra

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### Abstract

**Background:** Recent years have witnessed that there is a revival of interest in drug discovery from medicinal plants for the maintenance of health in all parts of the world. The aim of this work was to investigate 26 plants belonging to 17 families collected from a unique place in Yemen (Soqatra Island) for their in vitro anticancer, antimicrobial and antioxidant activities.

**Methods:** The 26 plants were extracted with methanol and hot water to yield 52 extracts. Evaluation for in vitro anticancer activity was done against three human cancer cell lines (A-427, 5637 and MCF-7) by using an established microtiter plate assay based on cellular staining with crystal violet. Antimicrobial activity was tested against three Gram-positive bacteria, two Gram-negative bacteria, one yeast species and three multiresistant *Staphylococcus* strains by using an agar diffusion method and the determination of MIC against three Gram-positive bacteria with the broth micro-dilution assay. Antioxidant activity was investigated by measuring the scavenging activity of the DPPH radical. Moreover, a phytochemical screening of the methanolic extracts was done.

**Results:** Notable cancer cell growth inhibition was observed for extracts from *Ballochia atro-virgata*, *Eureiandra balfourii* and *Hypoestes pubescens*, with IC<sub>50</sub> values ranging between 0.8 and 8.2 µg/ml. The methanol extracts of *Acanthospermum hispidum*, *Boswellia dioscorides*, *Boswellia socotrana*, *Commiphora ornifolia* and *Euphorbia socotrana* also showed noticeable antiproliferative potency with IC<sub>50</sub> values < 50 µg/ml. The greatest antimicrobial activity was exhibited by extracts from *Acacia pennivenia*, *Boswellia dioscorides*, *Boswellia socotrana*, *Commiphora ornifolia*, *Euclea divinorum*, *Euphorbia socotrana*, *Leucas samhaensis*, *Leucas virgata*, *Rhus thyriflora*, and *Teucrium sokotranum* with inhibition zones > 15 mm and MIC values ≤ 250 µg/ml. In addition, the methanolic extracts of *Acacia pennivenia*, *Boswellia dioscorides*, *Boswellia socotrana* and *Commiphora ornifolia* showed good antioxidant potential at low concentrations (more than 80% at 50 µg/ml).

**Conclusion:** Our results show once again that medicinal plants can be promising sources of natural products with potential anticancer, antimicrobial and antioxidative activity. The results will guide the selection of some plant species for further pharmacological and phytochemical investigations.

## Background

The worldwide use of natural products including medicinal plants has become more and more important in primary health care especially in developing countries. Many pharmacognostical and pharmacological investigations are carried out to identify new drugs or to find new lead structures for the development of novel therapeutic agents for the treatment of human diseases such as cancer and infectious diseases [1]. In developing countries and particularly in Yemen, a large segment of the population still rely on folk medicine to treat serious diseases including infections, cancers and different types of inflammations.

The Soqatra Archipelago in Yemen has long been a land of mystery. Over the centuries travelers returned from the Indian Ocean isles with bizarre tales of trees yielding dragon's blood and cucumbers, forests of frankincense and towering pinnacles shrouded in mist [2]. Soqatra is considered the "jewel" of biodiversity in the Arabian Sea. The long geological isolation of the Soqatra archipelago and its fierce heat and many droughts have combined to create a unique and spectacular endemic flora. Surveys have revealed that more than a third of the 800 or so plant species of Soqatra are found nowhere else [2]. Botanists rank the flora of Soqatra among the ten most endangered island flora in the world.

Currently, there is insufficient scientific research on the plants from Soqatra. In previous studies we described investigations of some endemic and non-endemic plants from the island Soqatra for their antimicrobial [3], antiviral [4], enzyme-inhibitory [5] and anticancer activity [6]. Since a literature search indicated the absence of further information regarding biological and phytochemical investigations of plants from Soqatra, this study was carried out as a part of our continued exploration of Yemeni medicinal plants for interesting biological activities. Thus, the main aim of the present project was to carry out a phytochemical and biological investigation on selected plants from the island of Soqatra, especially on those that are endemic and those that find use in the traditional medicine. In this study, 26 plants belonging to 17 families were collected for evaluation of their cytotoxic, antimicrobial and antioxidant activities and the main chemical contents.

## Methods

### Plant materials

The plants (Table 1) were collected from different locations of the island of Soqatra in the Winter of 2006 and identified at the Pharmacognosy Department, Faculty of Pharmacy, Sana'a University. Part of the identification of the investigated plants was done by Dr. Anthony G. Miller from the Royal Botanic Garden at Edinburgh, UK.

Voucher specimens were deposited at the Pharmacognosy Department, Faculty of Pharmacy, Sana'a University.

### Extraction of plant materials

The air-dried and powdered plant materials (10 g of each) were extracted with 400 ml methanol (CH<sub>3</sub>OH) by Soxhlet extraction for 8 hours. The residue was dried over night and then extracted with 250 ml water (H<sub>2</sub>O) by using a shaking water-bath at 70°C for 2 hours. The obtained methanolic and water extracts were filtered and evaporated by using a rotary evaporator and freeze dryer. The dried extracts were stored at -20°C until used.

### Determination of antimicrobial activity

#### Test organisms

The following microorganisms were used as test organisms in the screening: 3 Gram-positive strains namely, *Staphylococcus aureus* (ATCC 6538), *Bacillus subtilis* (ATCC 6059), *Micrococcus flavus* (SBUG 16), 2 Gram-negative strains namely, *Escherichia coli* (ATCC 11229), *Pseudomonas aeruginosa* (ATCC 27853) and one fungal strain *Candida maltosa* (SBUG 700). In addition, three multiresistant *Staphylococcus* strains namely, *Staphylococcus epidermidis* 847, *Staphylococcus haemolyticus* 535, and *Staphylococcus aureus* North German Epidemic Strain (supply from the Institute of Hygiene of Mecklenburg-Vorpommern, Greifswald, Germany) were also employed as test organisms. Stock cultures were maintained at 4°C on slopes of nutrient agar. The cultures were diluted to achieve optical densities corresponding to  $2.0 \times 10^6$  colony forming units (CFU/ml) for bacterial and  $2.0 \times 10^5$  spore/ml for fungal strains.

#### Antimicrobial assay

The disc-diffusion assay [7] was used to determine the antimicrobial potential of the investigated extracts. Nutrient agar (OXOID LTD, Basingstoke, Hampshire, England) was prepared by dissolving of 27 g/l in water. The sterile nutrient agar was inoculated with microbial cells (200 µl of microbial cell suspension in 20 ml agar medium) and poured into sterile petri dishes. Sterile filter paper discs of 6 mm diameter (Schleicher and Schuell, ref. No. 10321260, lot. DG0274-1) were impregnated with 20 µl of the extract solution (equivalent to 4 mg of the dried extract). The paper discs were dried and placed on the surface of the inoculated agar plates. Plates were kept for 2 hours in refrigerator to enable prediffusion of the extracts into the agar. Then the plates were incubated overnight (18 hours) at 37°C. In contrast, *M. flavus* was incubated at room temperature for 48 h and *C. maltosa* was incubated at 28°C for 48 h. Ampicillin, gentamicin and amphotericin B were used as positive control. Negative controls were performed with paper discs loaded with 20 µl of organic solvents (methanol and 5% ethanol) and dried. At the end of the incubation period the antimicrobial

**Table 1: List of plants screened in the study.**

Plant	Voucher specimen no.	Family	Part tested	Traditional uses <sup>a</sup>
<i>Acacia pennivenia</i> * Schweinf.	Mo-Sq28	Mimosaceae	L	As a paste around the breast for women with mastitis
<i>Acanthospermum hispidum</i> DC.	Mo-Sq10	Astraceae	L	Unknown
<i>Acridocarpus socotranus</i> * Oliv.	Mo-Sq16	Malpighiaceae	L, S	Headaches, paralysis and muscle or tendon pain
<i>Aloe perryi</i> * Baker	Mo-Sq9	Aloaceae	R	For eye and stomach problems, constipation and malaria
<i>Ballochia atro-virgata</i> * Balf.f.	Mo-Sq15	Acanthaceae	S, L	Unknown
<i>Blepharis spiculifolia</i> * Balf.f.	Mo-Sq13	Acanthaceae	L, S	Unknown
<i>Boswellia dioscorides</i> * Thulin & Gifri	Mo-Sq26	Burseraceae	B	Common cold, bronchitis, asthma and rheumatism
<i>Boswellia socotrana</i> * Balf.f.	Mo-Sq24	Burseraceae	B	As <i>Boswellia dioscorides</i>
<i>Capparis cartilaginea</i> Decne.	Mo-Sq8	Capparaceae	L	To treat itching, shortness of breath, head cold and for tumors
<i>Commiphora ornifolia</i> * (Balf.f.) Gillett	Mo-Sq23	Burseraceae	B	Antiseptic, diarrhea, dysentery and emmenagogue
<i>Corchorus erodioides</i> * Balf.f.	Mo-Sq27	Tiliaceae	L, F	Diuretic and urinary tract infections
<i>Croton socotranus</i> * Balf.f.	Mo-Sq4	Euphorbiaceae	L, T	For wounds
<i>Euclea divinorum</i> Hiern	Mo-Sq1	Ebenaceae	R	For oral care, tooth ache, fungal diseases, sores, wounds and abscesses
<i>Euphorbia socotrana</i> * Balf.f.	Mo-Sq5	Euphorbiaceae	L	For skin diseases and wounds
<i>Eureiandra balfourii</i> * Cogn.	Mo-Sq3	Cucurbitaceae	L	Unknown
<i>Ficus cordata</i> Thunb.	Mo-Sq4	Moraceae	L	Antiseptic and for ulcers and wounds
<i>Glossonema revoili</i> Franch.	Mo-Sq29	Asclepiadaceae	L, F	Increase milk production in breastfeeding women
<i>Hibiscus noli-tangere</i> * A.G.Mill.	Mo-Sq30	Malvaceae	L, R	For snake bite and fever in children
<i>Hypoestes pubescens</i> * Balf.f.	Mo-Sq12	Acanthaceae	L	Fungal skin diseases and scabies
<i>Lannea transulta</i> * (Balf.f.) Radcl.-Sm.	Mo-Sq17	Anacardiaceae	L	Haemostatic for wounds, and sores and abrasions
<i>Leucas samhaensis</i> * Cortes-Burns & A.G.Mill.	Mo-Sq23	Labiatae	L	For cough and cold
<i>Leucas virgata</i> * Balf.f.	Mo-Sq21	Labiatae	L	For persons with heartburn and indigestion and stomach problems
<i>Lycium sokotranum</i> * Wagner & Vierh.	Mo-Sq20	Solanaceae	L, S	For stomach ailments and encourage the wound healing
<i>Maerua angolensis</i> DC.	Mo-Sq7	Capparaceae	L	To treat fever, aches and general malaise
<i>Rhus thyriflora</i> * Balf.f.	Mo-Sq18	Anacardiaceae	T, L	To treat anorexia, general tonic and for painful joints
<i>Teucrium sokotranum</i> * Vierh.	Mo-Sq22	Labiatae	F, L	As flavoring agent and for indigestion

\* endemic plant, B: Bark, F: Flower, L: Leaves, R: Roots or rhizomes, S: Stems, T: Fruits

<sup>a</sup> Most of the information of traditional use has been taken from [2] and native people.

activity was evaluated by measuring the inhibition zones (diameter of inhibition zone plus diameter of the disc). An inhibition zone of 15 mm or more was considered as high antibacterial activity.

#### Broth micro-dilution assay for minimum inhibitory concentrations (MIC)

The broth micro-dilution method described by [8] with modifications was used to determine the MIC of extracts against the three standard Gram-positive strains. With sterile round-bottom 96-well plates, duplicate two-fold serial dilutions of extract (100 µl/well) were prepared in the appropriate broth containing 5% (v/v) DMSO to produce a concentration range of 2000 to 15.6 µg of extract/ml. Two-fold dilutions of ampicillin were used as a positive control. A bacterial cell suspension (prepared in the

appropriate broth) of 100 µl, corresponding to  $1 \times 10^6$  CFU/ml, was added in all wells except those in columns 10, 11 and 12, which served as saline, extract and media sterility controls, respectively. Controls for bacterial growth without plant extract were also included on each plate. The final concentration of bacteria in the assay was  $5 \times 10^5$  CFU/ml. The final concentration of extracts ranged between 1000 to 7.8 µg/ml. Plates were then incubated at 37°C for 18 h overnight. After incubation, the MIC of each extract was determined as the lowest concentration at which no growth was observed in the duplicate wells. Twenty microliters of a p-iodonitro-tetrazolium violet solution (0.04%, w/v) (Sigma, USA) was then added to each well. The plates were incubated for a further 30 min, and estimated visually for any change in color from yellow to pink indicating reduction of the dye due to bacte-

rial growth. The highest dilution (lowest concentration) that remained yellow corresponded to the MIC. Experiments were performed in duplicate.

#### Determination of anticancer activity-Cytotoxicity assay on human cancer cell lines

For the estimation of the *in vitro* cytotoxic potency of the investigated extracts, an established microtiter plate assay [9] was used with three human cancer cell lines: one lung cancer (A-427), one urinary bladder cancer (5637) and one breast cancer (MCF-7) line. Cell lines were obtained from the DMSZ, Braunschweig, Germany, and culture in RPMI 1640 medium with 10% FCS. Cytotoxicity determinations are based on cellular staining with crystal violet and were performed as previously described in detail. Briefly, a volume of 100  $\mu$ l of a cell suspension was seeded into 96-well microliter plates at a density of 1000 cell/well. Twenty-four hours later, cells were treated with the plant extracts at five dilutions and exposed continuously to the extracts for the next 96 h. Etoposide was used as a positive control. At the end of the exposure time, the medium was removed and the cells were fixed with a glutaraldehyde solution. The cells were then stained with crystal violet and the optical density (OD) was measured at  $\lambda = 570$  nm with a plate reader. The percent growth values were calculated by the following equation:

$$\text{Growth (\%)} = \frac{\text{OD}_T - \text{OD}_{c_0}}{\text{OD}_c - \text{OD}_{c_0}} \times 100$$

Where  $\text{OD}_T$  is the mean absorbance of the treated cells,  $\text{OD}_c$  is the mean absorbance of the controls,  $\text{OD}_{c_0}$  is the mean absorbance at the time the extract was added. The  $\text{IC}_{50}$  values were estimated by a linear least-squares regression of the growth values versus the logarithm of the extract concentration; only concentrations that yielded growth values between 10% and 90% were used in the calculation.

#### Determination of antioxidant activity (Scavenging Activity of DPPH Radical)

The DPPH free radical scavenging assay was carried out for the evaluation of the antioxidant activity. This assay measures the free radical scavenging capacity of the investigated extracts. DPPH is a molecule containing a stable free radical. In the presence of an antioxidant, which can donate an electron to DPPH, the purple colour typical for free DPPH radical decays, and the absorbance change at  $\lambda = 517$  nm is measured. This test provides information on the ability of a compound to donate a hydrogen atom, on the number of electrons a given molecule can donate, and on the mechanism of antioxidant action. The method was carried out as previously described by [10]. The methanolic and aqueous extracts were redissolved in methanol and 5% ethanol, respectively, and various concentrations (10, 50, 100, 500 and 1000  $\mu$ g/ml) of each extract were

used. Similar concentrations of ascorbic acid were used as positive control. The assay mixture contained in a total volume of 1 ml, 500  $\mu$ l of the extract, 125  $\mu$ l prepared DPPH (1 mM in methanol) and 375  $\mu$ l solvent (methanol or 5% ethanol). After 30 min incubation at 25°C, the decrease in absorbance was measured at  $\lambda = 517$  nm. The radical scavenging activity was calculated from the equation:

$$\% \text{ of radical scavenging activity} = \frac{\text{Abs}_{\text{control}} - \text{Abs}_{\text{sample}}}{\text{Abs}_{\text{control}}} \times 100$$

#### Phytochemical screening of the methanolic extracts

The screening of chemical constituents was carried out with the methanol extracts by using chemical methods and thin-layer chromatography (TLC) using different mixtures of organic solvents as mobile phases. Several chemical reagents e.g. Dragendorff's reagent for alkaloids, borntraeger reagent for anthraquinones and etc. were used in the detection according to previously published methodology [11].

## Results

In the course of our screening for the antimicrobial, anti-cancer, and antioxidant and activities, a number of plants from different locations of the island Soqatra used in Yemeni traditional medicine were evaluated. A total of 52 extracts representing 26 plant species belonging to 17 families were submitted to biological screening. The botanical names, plant part used and the traditional uses of the plants in the collected areas are presented in Table 1.

#### Antimicrobial activity

Table 2 shows the results of the antimicrobial activity of the investigated extracts in agar diffusion method. An inhibition zone > 15 mm was considered as a high antimicrobial activity. It was observed that the antimicrobial activity of the studied plant extracts was exhibited mainly against the Gram-positive bacteria. Consequently, the MIC-values were determined only against Gram-positive bacteria. The MIC values are reported in Table 3. In a general, among the investigated extracts the methanolic extracts exhibited the greatest antimicrobial effect.

Only rarely do plants shown antimicrobial activity against Gram-negative bacteria and *Candida maltosa* except *Acacia penninvenia*, *Boswellia* species and *Euclea divinorum*. It was apparent that the multiresistant *Staphylococcus* strains demonstrate more sensitivity to the investigated extracts than the other antibiotic susceptible Gram-positive bacteria (Table 2). Moreover, it was found that with the exception of *Boswellia* species, *Euclea divinorum* and *Hypoestes pubescens* no extract showed antifungal activity against *Candida maltosa* (Table 2). The most pronounced activity

**Table 2: Antimicrobial activity of the investigated plants in agar diffusion test.**

Plant species	Extracts	Extract yield in %	Microbial strains tested						Multiresistant strains tested		
			S. a.	B. c.	M. f.	E. c.	P. e.	C. m.	S. e. 847	S. h. 535	S. a. NGR
<i>Acacia pennivenia</i>	Methanolic	12.18	22	12	22	16	14	-	18	14	20
	Hot aqueous	5.97	20	-	20	-	-	-	8	-	18
<i>Acanthospermum hispidum</i>	Methanolic	16.14	16	-	22	-	-	-	18	12	20
	Hot aqueous	7.22	12	-	15	-	-	-	8	-	12
<i>Acridocarpus socotranus</i>	Methanolic	10.46	15	-	16	-	-	-	14	10	14
	Hot aqueous	4.75	18	-	16	-	-	-	18	14	22
<i>Aloe perryi</i>	Methanolic	20.27	-	-	-	-	-	-	18	10	20
	Hot aqueous	18.82	-	-	-	-	-	-	-	-	14
<i>Ballochia atro-virgata</i>	Methanolic	14.91	12	-	-	-	-	-	10	-	16
	Hot aqueous	5.70	12	-	-	-	-	-	-	-	-
<i>Blepharis spiculifolia</i>	Methanolic	5.04	12	-	-	-	-	-	10	-	16
	Hot aqueous	5.51	-	-	-	-	-	-	-	-	-
<i>Boswellia dioscorides</i>	Methanolic	40.45	18	16	20	8	10	10	28	18	38
	Hot aqueous	14.31	11	8	12	-	-	-	28	16	28
<i>Boswellia socotrana</i>	Methanolic	33.77	31	21	27	14	20	22	28	20	28
	Hot aqueous	11.68	25	12	16	10	15	16	22	18	24
<i>Capparis cartilaginea</i>	Methanolic	8.33	10	-	-	-	-	-	-	-	-
	Hot aqueous	10.02	-	-	-	-	-	-	-	-	-
<i>Commiphora ornifolia</i>	Methanolic	19.50	16	13	19	-	-	-	18	14	18
	Hot aqueous	10.72	11	8	12	-	-	-	18	10	20
<i>Corchorus erodioides</i>	Methanolic	10.46	10	9	12	-	-	-	-	-	-
	Hot aqueous	4.95	-	-	11	-	-	-	-	-	-
<i>Croton socotranus</i>	Methanolic	14.91	10	8	15	-	-	-	18	10	24
	Hot aqueous	6.78	-	-	-	-	-	-	20	10	24
<i>Euclea divinorum</i>	Methanolic	21.85	24	12	18	11	15	10	24	16	26
	Hot aqueous	4.13	16	-	-	-	-	-	12	-	20
<i>Euphorbia socotrana</i>	Methanolic	19.74	16	11	18	-	-	-	20	12	26
	Hot aqueous	11.75	-	-	-	-	-	-	20	12	26
<i>Eureiandra balfourii</i>	Methanolic	11.60	10	-	-	-	-	-	-	-	-
	Hot aqueous	8.58	12	-	15	-	-	-	-	-	-
<i>Ficus cordata</i>	Methanolic	9.06	10	-	-	-	-	-	-	-	12
	Hot aqueous	10.50	16	-	-	-	-	-	-	-	14
<i>Glossonema revoili</i>	Methanolic	16.34	20	-	-	-	-	-	-	-	-
	Hot aqueous	8.53	9	-	-	-	-	-	-	-	-
<i>Hibiscus noli-tangere</i>	Methanolic	10.61	10	-	-	-	-	-	-	-	-
	Hot aqueous	4.92	-	-	-	-	-	-	-	-	-
<i>Hypoestes pubescens</i>	Methanolic	21.16	8	-	-	-	-	15	-	-	-
	Hot aqueous	7.80	15	-	14	-	-	12	-	-	-
<i>Lannea transulta</i>	Methanolic	8.04	13	-	14	-	-	-	16	-	16
	Hot aqueous	9.15	14	-	16	-	-	12	22	12	22
<i>Leucas samhaensis</i>	Methanolic	11.47	-	-	20	-	-	-	14	12	18
	Hot aqueous	5.25	19	14	24	-	-	-	18	14	20
<i>Leucas virgata</i>	Methanolic	14.11	18	11	17	-	-	-	16	12	22
	Hot aqueous	3.37	17	-	15	-	-	-	20	12	26
<i>Lycium sokotranum</i>	Methanolic	10.93	20	-	15	-	-	-	12	12	20
	Hot aqueous	5.05	17	-	-	-	-	-	-	-	20
<i>Maerua angolensis</i>	Methanolic	22.01	-	-	-	-	-	-	-	-	-
	Hot aqueous	13.80	-	-	-	-	-	-	12	-	16
<i>Rhus thyriflora</i>	Methanolic	5.88	20	12	18	-	-	-	18	14	24
	Hot aqueous	11.50	20	12	21	-	-	-	20	16	26
<i>Teucrium sokotranum</i>	Methanolic	12.42	17	14	22	-	-	-	14	10	16
	Hot aqueous	4.43	22	10	15	-	-	-	18	14	20
Ampicillin 10 µg/disc			28	24	30	N.T.	N.T.	N.T.	-	-	-
Gentamicin 10 µg/disc			N.T.	N.T.	N.T.	15	17	N.T.	N.T.	N.T.	N.T.
Amphotericin 10 µg/disc			N.T.	N.T.	N.T.	N.T.	N.T.	10	N.T.	N.T.	N.T.

with inhibition zones greater than 15 mm was found with the methanolic extracts of 10 plants (Table 2). The most effective plant was *Boswellia socotrana*, of which the methanolic and aqueous extracts demonstrated the greatest antimicrobial effect against all tested microorganisms (Table 2). The lowest MIC values were obtained against *Staphylococcus aureus* and *Micrococcus flavus* by the methanolic extracts of *Boswellia* species (125 µg/ml) (Table 3).

#### **In vitro anticancer activity**

Table 4 presents the IC<sub>50</sub> values for the in vitro cytotoxic activity of the investigated 26 methanolic extracts. From our experience, the most aqueous extracts don't show any notable in vitro anticancer effect at the highest concentration tested (50 µg/ml). Generally, the aqueous extracts may exhibit only a weak cytotoxic effect starting with a concentration of 250 µg/ml. Thus, these extracts were excluded in our screen. The results in Table 4 demonstrate that out of the 26 investigated plants (only methanolic extracts) three plant extracts had noteworthy cytotoxic effects in all three cell lines tested, namely: *Ballochia atrovirgata* (IC<sub>50</sub> between 1.5 and 2.8 µg/ml), *Eureiandra balfourii* (IC<sub>50</sub> between 0.8 and 3.4 µg/ml) and *Hypoestes pubescens* (IC<sub>50</sub> between 4.8 and 8.2 µg/ml) (Table 4). Moreover, the extracts of *Acanthospermum hispidum*, *Boswellia dioscorides*, *Boswellia socotrana*, *Commiphora ornifolia* and *Euphorbia socotrana* exhibited a pronounced cytotoxic effect against all tested cell lines ((IC<sub>50</sub> between 9.3 and 38.5 µg/ml). The other plant extracts demonstrated no significant cytotoxic effect at the highest tested concentration of 50 µg/ml.

#### **Radical scavenging activity**

The methanol extracts of seven plants, namely: *Acacia pennivenia*, *Acridocarpus socotranus*, *Boswellia dioscorides*, *Boswellia socotrana*, *Commiphora ornifolia*, *Euphorbia socotrana*, and *Lannea transulta* showed a high effective free radical scavenging in the DPPH assay (Table 3). These extracts exhibited a noticeable antioxidant effect at low concentrations (Table 3). So the methanolic extracts of *Acacia pennivenia*, *Boswellia dioscorides*, *Boswellia socotrana* and *Commiphora ornifolia* exhibited a great antioxidant effect at 50 µg/ml (78, 89, 88% and 85%, respectively), comparing with the effect of ascorbic acid at this concentration (Table 3). The hot aqueous extracts of all investigated plants showed only weak antioxidant effect (Table 3).

#### **Phytochemical screening**

The results of the phytochemical screening of the investigated methanolic extracts indicated the presence of different types of active constituents like flavonoids, terpenoids, tannins, volatile oils, etc... (Table 4).

## **Discussion**

In continuation of our search for substances of plant origin with pharmacological effects, we have screened 26 plants collected from the island Soqatra, Yemen for their antimicrobial, cytotoxic and antioxidant activities and for their chemical content. It is important to mention that this work represents the first report on the antimicrobial, cytotoxic and antioxidant activities of extracts from 20 endemic plants (Table 1). The existing knowledge about the other six investigated plants is in many cases very limited.

A correlation was found between the antibacterial activity observed by agar diffusion assay and MIC determination. It is interesting to note that these plant extracts showed more activity on multi-drug resistant *Staphylococcus* strains than the antibiotic susceptible Gram-positive bacteria.

It was demonstrated previously that alcoholic extract of different species of *Acacia* like *A. arabica*, *A. nilotica* and *A. auriculiformis* have antibacterial activity [12-15], and that the isolated saponines from *A. auriculiformis* were responsible for the noticed effect [15]. Previous work indicated that both bark and heartwood extracts of *A. confusa* clearly have strong antioxidant effects [16]. Phenolic compounds were isolated from the bark of *A. confusa*, which were mainly responsible for the antioxidant effect of this plant [17]. Furthermore, triterpenoid saponins were isolated from *A. victoriae*, which induced decreased tumor cell proliferation and induced apoptosis [18]. In addition, a significant reduction in the values of tumor burden and tumor incidence was observed in mice treated by oral gavage with the *A. nilotica* gum and leaf extracts [19]. The antimicrobial and antioxidant effects we have found with extracts from *A. pennivenia* are in accordance with these data. The phytochemical screening revealed the presence of saponins and phenolic compounds like tannins in the methanolic extract of *A. pennivenia*, which could be responsible for these activities. On the other hand, our results of cytotoxic activity were not in agreement with the anticancer effect noted with other *Acacia* species; i.e., at the highest concentration used in our screening (50 µg/ml), the extracts of *A. pennivenia* exhibit no cytotoxic activity.

The antimicrobial effect of leaves and flowers extracts of *Acanthospermum hispidum* has been previously investigated [20]. Moreover, the isolation of sesquiterpene lactones was reported [21,22]. Our screening results confirmed the antimicrobial effect of the alcoholic extract. The hot aqueous extract exhibited a moderate antibacterial effect in contrast with data presented earlier [20]. In addition, the methanolic extract brought about a pronounced growth inhibitory effect against all tested cancer

**Table 3: Free radical scavenging activity and MIC of the investigated plants.**

Plant species	Extracts	Radical scavenging activity in %					MIC in µg/ml		
		10 (µg/ml)	50 (µg/ml)	100 (µg/ml)	500 (µg/ml)	1000 (µg/ml)	<i>S. aureus</i>	<i>B. subtilis</i>	<i>M. flavus</i>
<i>Acacia pennivenia</i>	Methanolic	25.4	78.5	88.9	95.0	94.0	250	500	250
	Hot aqueous	4.8	29.2	31.1	42.8	67.0	500	1000	500
<i>Acanthospermum hispidum</i>	Methanolic	2.8	13.8	25.9	55.5	94.7	500	1000	500
	Hot aqueous	5.2	11.6	14.4	26.3	27.4	> 1000	> 1000	> 1000
<i>Acridocarpus socotranus</i>	Methanolic	5.1	40.8	80.9	92.6	94.6	250	1000	250
	Hot aqueous	0.6	6.7	37.6	46.5	45.3	250	> 1000	250
<i>Aloe perryi</i>	Methanolic	6.7	19.8	28.7	92.4	94.1	> 1000	> 1000	> 1000
	Hot aqueous	2.1	6.4	20.8	36.4	45.9	> 1000	> 1000	> 1000
<i>Ballochia atro-virgata</i>	Methanolic	2.1	5.3	45.7	56.8	94.2	> 1000	> 1000	> 1000
	Hot aqueous	2.0	2.7	34.5	43.7	36.7	> 1000	> 1000	> 1000
<i>Blepharis spiculifolia</i>	Methanolic	14.8	13.3	25.1	64.6	91.5	> 1000	> 1000	> 1000
	Hot aqueous	1.6	4.4	34.3	38.3	46.8	> 1000	> 1000	> 1000
<i>Boswellia dioscorides</i>	Methanolic	25.8	89.8	96.1	96.3	96.8	125	500	125
	Hot aqueous	7.8	39.0	65.9	68.2	74.6	500	1000	500
<i>Boswellia socotrana</i>	Methanolic	26.1	88.2	94.6	94.9	95.1	125	250	125
	Hot aqueous	2.9	30.9	58.5	62.1	75.8	250	500	250
<i>Capparis cartilaginea</i>	Methanolic	0.2	3.8	2.1	51.2	87.6	> 1000	> 1000	> 1000
	Hot aqueous	3.1	1.1	22.8	27.5	28.2	> 1000	> 1000	> 1000
<i>Commiphora ornifolia</i>	Methanolic	20.8	85.9	95.0	95.4	95.2	250	500	250
	Hot aqueous	10.6	25.2	49.1	66.2	72.9	500	1000	500
<i>Corchorus erodioides</i>	Methanolic	10.4	14.3	27.6	95.1	94.1	> 1000	> 1000	> 1000
	Hot aqueous	4.2	5.1	37.6	57.9	59.7	> 1000	> 1000	> 1000
<i>Croton socotranus</i>	Methanolic	5.3	12.6	22.2	78.9	93.1	500	1000	500
	Hot aqueous	2.0	2.9	10.1	23.5	26.4	> 1000	> 1000	> 1000
<i>Euclea divinorum</i>	Methanolic	3.1	10.6	36.2	93.1	88.6	250	1000	500
	Hot aqueous	14.3	27.1	41.5	52.6	56.1	> 1000	> 1000	> 1000
<i>Euphorbia socotrana</i>	Methanolic	16.7	67.4	95.5	96.3	95.2	500	1000	500
	Hot aqueous	1.9	8.8	28.7	36.2	40.1	> 1000	> 1000	> 1000
<i>Eureiandra balfourii</i>	Methanolic	15.0	17.8	8.3	19.1	57.7	> 1000	> 1000	> 1000
	Hot aqueous	7.3	23.0	35.4	42.7	41.0	> 1000	> 1000	> 1000
<i>Ficus cordata</i>	Methanolic	2.5	12.5	31.0	89.2	91.6	> 1000	> 1000	> 1000
	Hot aqueous	1.6	9.3	16.4	18.9	20.4	> 1000	> 1000	> 1000
<i>Glossonema revouili</i>	Methanolic	1.7	14.9	26.8	38.6	76.4	> 1000	> 1000	> 1000
	Hot aqueous	0.3	2.7	2.5	7.8	8.1	> 1000	> 1000	> 1000
<i>Hibiscus noli-tangere</i>	Methanolic	0.6	7.3	18.4	85.9	89.0	> 1000	> 1000	> 1000
	Hot aqueous	1.4	0.8	2.8	5.6	6.6	> 1000	> 1000	> 1000
<i>Hypoestes pubescens</i>	Methanolic	1.5	4.0	16.6	38.7	72.6	> 1000	> 1000	> 1000
	Hot aqueous	2.6	4.2	3.1	16.1	18.3	1000	> 1000	500
<i>Lannea transulta</i>	Methanolic	21.9	64.2	95.4	92.1	98.6	1000	> 1000	1000
	Hot aqueous	36.7	33.2	37.2	32.3	29.9	1000	> 1000	1000
<i>Leucas samhaensis</i>	Methanolic	2.3	9.6	8.0	61.7	88.8	> 1000	> 1000	500
	Hot aqueous	3.8	5.6	37.3	49.3	47.1	500	1000	500
<i>Leucas virgata</i>	Methanolic	1.5	1.1	2.8	27.6	81.9	500	> 1000	1000
	Hot aqueous	26.2	34.8	39.5	44.0	51.9	500	> 1000	500
<i>Lycium sokotranum</i>	Methanolic	5.6	27.8	29.8	91.4	94.2	500	1000	500
	Hot aqueous	26.5	30.3	31.2	37.4	39.5	1000	> 1000	> 1000
<i>Maerua angolensis</i>	Methanolic	13.8	19.3	32.0	52.5	82.3	> 1000	> 1000	> 1000
	Hot aqueous	29.1	65.1	69.1	68.3	73.9	> 1000	> 1000	> 1000
<i>Rhus thyrsoiflora</i>	Methanolic	3.8	29.4	55.9	95.6	95.4	500	> 1000	500
	Hot aqueous	1.1	9.3	12.8	22.4	30.5	500	1000	500
<i>Teucrium sokotranum</i>	Methanolic	3.4	2.8	16.4	41.0	92.1	500	1000	500
	Hot aqueous	24.2	28.7	38.2	47.6	61.4	250	1000	500
Ascorbic acid		42.8	94.2	96.8	96.6	96.9			

**Table 4: IC<sub>50</sub> values (µg/ml) for cell growth inhibition of the investigated methanolic extracts on three human cancer cell lines and phytochemical screening.**

Plant species	Extracts	Cell lines			Phytochemical screening
		5637	MCF-7	A-427	
<i>Acacia pennivenia</i>	Methanolic	> 50	> 50	> 50	Saponins, tannins
<i>Acanthospermum hispidum</i>	Methanolic	9.37 ± 1.98	19.92 ± 8.94	16.70 ± 2.32	Sesquiterpene lactones
<i>Acridocarpus socotranus</i>	Methanolic	> 50	> 50	> 50	Flavonoids, terpenoids
<i>Aloe perryi</i>	Methanolic	> 50	> 50	> 50	Anthraquinones, flavonoids
<i>Ballochia atro-virgata</i>	Methanolic	2.83 ± 2.06	2.94 ± 0.28	1.58 ± 0.54	Terpenoids
<i>Blepharis spiculifolia</i>	Methanolic	> 50	> 50	> 50	Phenolic compounds, terpenoids
<i>Boswellia discorides</i>	Methanolic	29.0 ± 8.26	> 50	27.60 ± 10.31	Volatile oil, terpenoids, flavonoids
<i>Boswellia socotrana</i>	Methanolic	18.4 ± 4.66	> 50	24.9 ± 8.73	Volatile oil, terpenoids, flavonoids
<i>Capparis cartilaginea</i>	Methanolic	> 50	> 50	> 50	Glucosinolates, flavonoids
<i>Commiphora ornifolia</i>	Methanolic	30.2 ± 3.12	38.5 ± 1.93	35.1 ± 3.15	Volatile oil, terpenoids, flavonoids
<i>Corchorus erodioides</i>	Methanolic	> 50	> 50	> 50	Flavonoids, phenolic compounds
<i>Croton socotranus</i>	Methanolic	> 50	> 50	> 50	Flavonoids, terpenoids, tannins
<i>Euclea divinorum</i>	Methanolic	> 50	> 50	> 50	Phenolic acids, tannins
<i>Euphorbia socotrana</i>	Methanolic	42.0 ± 7.43	> 50	38.1 ± 13.49	Terpenoids, flavonoids, steroids, tannins
<i>Eureiandra balfourii</i>	Methanolic	0.82 ± 0.15	3.47 ± 1.18	2.25 ± 0.57	Terpenoids, flavonoids
<i>Ficus cordata</i>	Methanolic	> 50	> 50	> 50	Tannins, terpenoids
<i>Glossonema revoili</i>	Methanolic	> 50	> 50	> 50	Steroids, flavonoids
<i>Hibiscus noli-tangere</i>	Methanolic	> 50	> 50	> 50	Tannins, lignans
<i>Hypoestes pubescens</i>	Methanolic	8.25 ± 3.49	7.03 ± 2.02	4.85 ± 1.70	Alkaloids, terpenoids
<i>Lannea transulta</i>	Methanolic	> 50	> 50	> 50	Tannins, flavonoids
<i>Leucas samhaensis</i>	Methanolic	> 50	> 50	> 50	Volatile oil, terpenoids and flavonoids
<i>Leucas virgata</i>	Methanolic	> 50	> 50	> 50	Volatile oil, terpenoids and flavonoids
<i>Lycium sokotranum</i>	Methanolic	> 50	> 50	> 50	Alkaloids
<i>Maerua angolensis</i>	Methanolic	> 50	> 50	> 50	Glucosinolates, tannins
<i>Rhus thyriflora</i>	Methanolic	> 50	> 50	> 50	Flavonoids, terpenoids, tannins
<i>Teucrium sokotranum</i>	Methanolic	> 50	> 50	> 50	Volatile oil, terpenoids
Etoposide (µM)		0.54 ± 0.30	0.50 ± 0.19	0.13 ± 0.10	

Values are averages and standard deviations of three or more independent determinations.

cell lines we tested it against. These effects are most likely due to the presence of sesquiterpene lactones identified in our phytochemical screening and in literature data.

Whereas the investigation of *Acridocarpus vivy* showed cytotoxic effect against some cancer cell lines [23], the methanolic extract of *Acridocarpus socotranus* demonstrated no cytotoxic activity in our screen. However the plant extract exhibited a strong antioxidant and moderate antibacterial effects. This finding may be correlated with the presence of flavonoids and terpenoids.

In contrast to Ali and co-workers [24], who found a promising antimicrobial effect for *Aloe perryi*, our extracts of *Aloe perryi* only showed activity against multiresistant bacteria. Although the phytochemical screening illustrated the presence of anthraquinones, which are mostly responsible for cytotoxic and antioxidant activity [25], our results do not indicate any cytotoxic activity at the highest concentration tested (50 µg/ml) and exhibited a moderate antioxidant effect only at high concentrations (500 and 1000 µg/ml).

It is important to consider that we found no published data on the genus *Ballochia* and *Eureiandra*. So this is the first report on pharmacological and chemical investigation of plants of these genera. The remarkable cytotoxic effect of both plants with IC<sub>50</sub> values between 0.8 and 3.4 µg/ml is significant. According to the criteria of the American National Cancer Institute, 30 µg/ml is the upper IC<sub>50</sub> limit considered promising for purification of a crude extract [26]. Therefore, the highest concentration tested (50 µg/ml) in our screening was slightly above this limit.

The chemical screening showed the presence of terpenoids in both plants (mainly diterpenoids and triterpenoids), which could be correlated with this effect. *E. balfourii* belongs to the family cucurbitaceae, plants of which are famous for their cytotoxic tetracyclic triterpenoids known as cucurbitacins [27-29]. This type of compounds could be responsible for the observed activity in *E. balfourii*.

In our previous studies, the antimicrobial effects of some *Boswellia* species namely *B. elongata* and *B. ameero* were



investigated [3]. It was found that both plants exhibited a strong antimicrobial effect only against Gram positive bacteria. Both plants demonstrated no cell growth inhibition on five human cancer cell lines [6]. Furthermore, it was reported that the extract of *B. serrata* showed an effect against some bacterial strains [30]. The antimicrobial activity and the chemical content of the volatile oil of some *Boswellia* species like *B. carteri*, *B. papyrifera*, *B. serrata* and *B. rivae* were determined [31]. It was shown that the oils consisted of several monoterpenes, sesquiterpenes and diterpenes are responsible for the effect observed. The *B. socotrana* and *B. dioscorides* we investigated produced extracts with the most effective activity against all tested microorganisms. The essential oils and the terpenoids determined in our phytochemical screening are mostly responsible for this effect. Besides this noticeable antimicrobial effect, the methanolic extracts manifested a considerable cytotoxic effect against two cell lines (5637 and A-427) with  $IC_{50}$  values between 18 and 29  $\mu\text{g/ml}$ . For this effect, boswellic acids, which may represent a considerable part of the chemical content, could contribute to this observed effect. Furthermore, both plants demonstrated even at low concentration (50  $\mu\text{g/ml}$ ) a remarkable radical scavenging effect (88 and 89%). This effect may be attributed to the present flavonoids.

Among the most interesting plants, *Commiphora ornifolia* showed similar antimicrobial activities with *Boswellia* plants. The same extract manifested a high antioxidant effect (85%) at 50  $\mu\text{g/ml}$ . The extracts and isolated compounds from *Commiphora opobalsamum* exhibited similar antimicrobial and antioxidant activities [32]. Thus, the estimated antimicrobial and antioxidant effects of our investigated *C. ornifolia* are in accordance with these data. Whereas no cytotoxic activity in *C. myrrha* was found [33], we observed an antiproliferative effect of the methanolic extract against all three cell lines with  $IC_{50}$  values between 30 and 38  $\mu\text{g/ml}$ . The determined effects of *C. ornifolia* are mostly attributed to the essential oil, flavonoids and triterpenes found in the methanolic extract.

Another interesting plant was *Euphorbia socotrana*, which demonstrated considerable antimicrobial, cytotoxic and antioxidant activities. Our data are in agreement with literature data of other *Euphorbia* species as *E. thymifolia*, *E. hirta* and *E. cheiradenia* [34-36]. Studies have demonstrated that some triterpenoids isolated from *Euphorbia* species are responsible for the antimicrobial effect and that some of these compounds were able to induce moderate apoptosis in at least one cancer cell line [37,38]. The presence of such terpenoids in our *E. socotrana* may explain the biological effects seen in our screens.

Some authors reported on investigation with some *Hypoestes* species, where the isolation of two cell growth

inhibitory phenanthroindolizidine alkaloids termed hypoestestatin 1 and hypoestestatin 2 from the East African shrub *H. verticillaris* was described [39]. In addition, several antifungal diterpenoids from *H. serpens* were isolated [40]. The methanolic extract of *H. pubescens* tested in our screens showed a remarkable antifungal effect against *Candida maltosa* and an extraordinary cytotoxic effect against all tested cancer cell lines. Apparently these observed activities are correlated with the presence of the terpenoids and alkaloids found in the phytochemical screening.

The notably antimicrobial effect of *Rhus thyrsoiflora* and *Teucrium sokotranum* was consistent with literature data of other *Rhus* and *Teucrium* species [41,42]. On the other hand, other authors noted a strong antioxidant effect of some *Teucrium* species and *R. coriaria*, which is not supported by results obtained in our screening [43,44]. Moreover, a cytotoxic activity for the sap of the lacquer tree *R. succedanea* was described previously [45], whereas the investigated *R. thyrsoiflora* showed no growth inhibitory effect on the tested cancer cell lines.

## Conclusion

In conclusion, the results in the present study are agreed to some extent with the traditional uses of the plants investigated. Our results further support the idea that medicinal plants can be promising sources of potential anticancer and antimicrobial agents and antioxidants. The present results will form the basis for selection of plant species for further investigation in the potential discovery of new natural bioactive compounds. Studies aimed at the isolation and structure elucidation of anticancer, antibacterial and antioxidant active constituents from some plants e.g. *Acacia penninvenia*, *Ballochia atro-virgata*, *Boswellia dioscorides*, *Boswellia socotrana*, *Commiphora ornifolia*, *Euphorbia socotrana*, *Eureiandra balfourii* and *Hypoestes pubescens* are in progress.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

RAM carried out the study design, plant collection, experimental work, data collection and interpretation, literature search and manuscript preparation. RG provided assistance in evaluation of the anticancer activity and data interpretation. UJL and PJB supervised the work, evaluated the data and corrected the manuscript for publication. All authors read and approved the final manuscript.

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