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Full Length Research Paper

Cytotoxic, antimicrobial and antioxidant activities and phytochemical analysis of *Artemisia judaica* and *A. sieberi* in Saudi Arabia

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Cancer and microbial infectious diseases are considered a global threat. Plants have been investigated across the world to exploit their potential anticancer and antimicrobial effective agents. In this study, two medicinal plant species native to Saudi Arabia, namely; *Artemisia judaica* and *Artemisia sieberi* were screened to assess their antioxidant, anticancer and antimicrobial potential activities as well as phytochemical compositions. The collected aerial parts were extracted by maceration with methanol. Cytotoxic and antimicrobial activities were investigated using the MTT and MIC assays, respectively. Free radical scavenging and antioxidant potential were assessed respectively by 2, 2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) methods. The total flavonoid and phenolic contents of the crude methanolic extract were quantified using standard methods. *Artemisia judaica* displayed a strong cytotoxicity compared to *A. sieberi* while both species showed approximately similar bacterial and fungal growth inhibition. In contrast, *A. sieberi* displayed the highest phenol and flavonoid contents between the two species which was consistent with the higher antioxidant activity found in *A. sieberi*. It is concluded that both *Artemisia* species could be a promising source of antioxidant, anticancer and antimicrobial agents.

Key words: *Artemisia judaica, Artemisia sieberi,* anticancer, antimicrobial.

INTRODUCTION

For millennia, plants have played a crucial role in preserving and enhancing humans' quality of life. Moreover, plants were and still represent a rich source of new therapeutic agents for the treatment of several primary health care ailments. In addition, there are several reports available where natural products have shown their promising potential to cure complex diseases (Newman and Cragg, 2016; Mushtaq et al., 2018; Thomford et al., 2018; Che and Zhang, 2019). In the area of cancer treatment, which now represents the most common and second most lethal disease in the world (Siegel et al., 2020), medicinal plants contribute to

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anticancer drugs that inhibit tumor progression without many side effects (Dall'Acqua, 2014; Khazir et al., 2014; Iqbal et al., 2017). Therefore, plants are still being investigated across the world to exploit their potential of anticancer agents. Moreover, microbial infectious diseases are also considered a global threat. Although a large number of new antibiotics have been introduced by pharmacological industries, the microbial resistance to them has increased (Darsanaki and Lisar, 2014). Therefore, increasing attention has turned to medicinal plant as a potential source of new antimicrobials (Ali-Shtayeh et al., 1998).

Artemisia (Asteraceae), popularly known as "Sage Brush" or "Wormwood," is a genus of small herbs and shrubs of about 500 species, which are mainly found in Asia, Europe and North America (Bora and Sharma, 2011) but occurs to a lesser extent in the southern hemisphere. It is widely used in folk medicine for several ailments, including coughing (Tan et al., 1998), lowering pain (Morshedi et al., 2011), reducing phlegm (Martínez et al., 2012) and hypertension (Ben-Nasr et al., 2013). Several studies conducted in this genus have revealed their potential in antimalarial, antinociception and antimicrobial activities (Zhang et al., 2017). *Artemisia judaica* (Arabic name, Shih Balady) is a fragranced shrub that grows widely in the Arabian area (Acheuk et al., 2017). This species is used as a tea in Egypt Sinai and Saudi Arabia. *A. judaica* has antioxidant (El-Massry et al., 2002), antibacterial (Liu et al., 2003), anti-malarial (Liu et al., 2004), and anti-inflammatory properties (El-Sayed et al., 2013). *Artemisia sieberi* on the other hand, is a perennial shrub that grows abundantly in arid areas of Middle Eastern countries (Abouhosseini et al., 2016) and other parts of the world (Shadi and Saharkhiz, 2016). It is used as anthelminthic in Middle East traditional medicine (Mahboubi, 2017) and to treat various diseases, including diabetes mellitus in Jordan (Irshaid et al., 2012). *A. sieberi* is also reported to be used as an herbal medicine for treating high blood pressure and gastrointestinal ailments (Bidgoli et al., 2013). Saudi Arabia has a diversity of plant species that grow in harsh conditions that make them medicinally promising (Osman et al., 2014). However, investigation into the biological properties of *Artemisia* genera in Saudi Arabia remains insufficient. Therefore, this investigation aims to report on the phytochemicals composition, antioxidant, cytotoxic as well as antimicrobial activities of *A. judaica* and *A. sieberi*. The study will be of value in highlighting the importance of *Artemisia* species as a natural resources for a novel compounds in addition to assert its beneficial effects in folk medicine.

MATERIALS AND METHODS

Plant collection and authentication

The aerial parts (leaves and stems) of *A. judaica and A. sieberi* were collected during winter season (February, 2015) from Al-Ghat, 230 km northwest of Riyadh, Saudi Arabia. Both *A. judaica* and *A. sieberi* were taxonomically certified by Prof. Ramzi Mothan, Pharmacognosy Department, King Saud University (KSU), Riyadh, Saudi Arabia (SA). Voucher specimens were deposited in the herbarium of the Department of Pharmacognosy.

Extracts preparation

The aerial parts of *A. judaica and A. sieberi* were dried at 45°C and grounded. 100 g of each plant powder was extracted with methanol (500 ml) using the maceration method. The liquid extract was concentrated under vacuum to get 11 g crude methanol extract for *A. sieberi* and 15 g crude methanol extract for *A. judaica,* both extracts were kept in a fridge until use.

Phytochemical analysis

Estimation of total phenol and flavonoid contents

Total phenolic content of *A. judaica* and *A. sieberi* extracts was determined by the standard Folin Ciocalteau spectrophotometric method (Slinkard and Singleton, 1977; Sulaiman et al., 2013). Briefly**,** 0.5 ml of each extract was added to 0.1 ml of Folin-Ciocalteau reagent (0.5 N) and the contents of the flask were mixed thoroughly. Later 2.5 ml of Sodium carbonate (Na_2CO_3) was added, mixed and incubated for 0.5 h. The optical density was measured at 760 nm utilizing UV-Visible spectrophotometer. The total phenolic contents were expressed as mg gallic acid equivalents (GAE)/g of the extract. For total flavonoids content, standard aluminium chloride spectrophotometric method according to Mervat et al. (2009) was used. In brief, 1 ml of each extract at a concentration of 1 mg/ml was taken. Then 1 ml of $AlCl_3$ (10%) was added sequentially. The test solution was vigorously shaken. Absorbance was recorded at 415 nm after 30 min of incubation. A standard calibration plot was generated at 415 nm using known concentrations of quercetin. From calibration plot, flavonoid concentrations in each sample were calculated and expressed as mg quercetin equivalent (QE) /g of the extract.

Antioxidant activity

DPPH radical-scavenging activity

A. judaica and *A. sieberi* antioxidative activity was estimated by DPPH (2, 2-diphenyl-1-picrylhydrazyl) method as reported by Brand-Williams et al. (1995) and Hussein et al. (2019). Various concentrations of *A. judaica* and *A. sieberi* extracts (10, 50, 100, 500 and 1000 µg/mL) were prepared. Thereafter, 0.5 mL of each concentration was mixed with 0.125 mL DPPH and 0.375 mL methanol and incubated for 0.5 h. The optical density was measured at λmax = 517 nm. Ascorbic acid was used as a positive control. Radical scavenging activity was calculated as the following formula:

% of radical scavenging activity = (Abs control - Abs extract / Abs control) × 100

ABTS radical cation scavenging activity

The antioxidative activity of *A. judaica* and *A. sieberi* was estimated utilizing ABTS method as reported by Li et al. (2009), with minor modification. Aqueous solutions of ABTS (7 mmol/L) and potassium persulfate (2.45 mmol/L) were prepared. After 12 h standing in the dark, the two solutions were mixed and incubated for 0.5 h,

followed by standing in refrigerator for 24 h, then diluted in ethanol. To ABTS solution 50 µg/ml (1:1) different prepared concentration of each extract (10, 50, 100, 500 and 1000 µg/mL) were pipetted to initiate the reaction for achieving a calibration curve. The absorbance was read at wavelength λ734 nm using UV-vis spectrophotometer. Ethanol (95%) was used as a blank. ABTS (50 µg/ml) solution was used as control. Ascorbic acid was used as standard. Three replicates for standard and each extract were used for analysis. The percentage of antioxidant capacity for each extract was determined based on the reduction of ABTS absorbance by calculation using the following formula (Li et al., 2011).

% of radical scavenging activity = (Abs control - Abs sample / Abs control) × 100

Cytotoxic activity (MTT assay)

To assess the effect of the *A. judaica* and *A. sieberi* extracts on the growth of different malignant cell lines (MCF-7 breast, LoVo colon and HepG2 liver) the MTT assay was performed according to Mothana et al. (2019). In brief, 50,000 cells/well were added into cell culture plate (24-well). After 24 h of incubation at 37°C with 5% CO_2, the cells were treated with methanolic extracts of *A. judaica* and *A. sieberi* at (0, 25, 50,100 and 200 µg/ mL) concentrations. The viability of the cells was determined after 48h. 100 µL of MTT (5 mg/mL) was added to each well and incubated for 4 h. The media was removed and 1000 µL of acidified isopropanol was pipetted into each well to solubilize the formazan crystals. The absorbance was then measured at 540 nm using a (Bio-Tek, USA) plate reader.

Determination of the antimicrobial activity

Test microorganisms

Two gram-positive bacteria *Staphylococcus aureus* (ATCC 25923) and *Enterococcus. faecalis* (ATCC 29212) and two gram-negative bacteria *Escherichia coli* (ATCC 25922) and *Proteus vulgaris* (ATCC 8427) and one fungal strain *Candida albicans* (ATCC 60193) were used in this investigation.

Minimum inhibitory concentrations

The minimum inhibitory concentrations (MICs) for methanolic extracts of *A. judaica* and *A. sieberi* was assessed using micro-well dilution method as previously method stated by Mann and Markham (1998) and Sulaiman (2013), with some modifications. To 96- sterile well plates, duplicate two-fold serial dilutions of each sample (100µL/well) were made in the required broth media containing 5% (v/v) DMSO to achieve 2000 to 31.2 mg/ml concentrations. Bacterial or fungal suspension (100 µL, 1106 CFU/ml) was then added. Thereafter, the plates were incubated at 37°C for 24 h and at 25°C and 72 h for bacterial and fungal strain respectively. The MIC of *A. judaica* and *A. sieberi* methanolic extracts were defined as the lowest concentration displaying no detectable bacterial or fungal growth. Gentamycin and nystatin were used as a positive control. For MBC and MFC estimation, 5µL from the wells that showed no growth was transferred to agar plates and further incubated for 24 or 72 h. MBC and MFC are the lowest concentrations that evidenced no visible bacterial or fungal growth.

Statistical analysis

Data represent the mean ± standard deviation of three determinations. The IC_{50} values of MTT assay were determined using OriginPro8.5 Software (Massachusetts, USA).

RESULTS

Total phenol and total flavonoid contents

Both *A. sieberi* and *A. judaica* showed different total phenolic and flavonoid content. As shown in Figure 1, *A. sieberi* exhibited higher total phenolic and flavonoid content (122.1 mg of GAE/g) powder weight than *A. judaica* which exhibited a lower total phenolic content (117.5 of GAE/g). Furthermore, *A. sieberi* showed higher flavonoid content (36.5 mg of QE/g) than that of *A. judaica* which showed a lower flavonoid content (28.7 of QE/g) equivalent.

Antioxidant activity

Both species showed dose dependent scavenging activities (Table 1). The results of this study reported that *A. sieberi* showed higher antioxidant activity than *A. judaica*.

Cytotoxic activity

Extracts of both species exhibited anti-proliferation activity in a dose dependent manner as illustrated by Figure 2. The calculated IC_{50} values ranged between 42 and 93 µg/ml (Table 2). However, *A. judaica* showed a higher effect against all cell lines than *A. sieberi,* and the activity was stronger against HepG2, followed by MCF-7 and finally LoVo.

Antimicrobial activity

MICs (Minimum inhibitory concentrations), MBCs (minimum bactericidal concentrations), and MFCs (minimum fungicidal concentrations) of *A. judaica* and *A. sieberi* are displayed in Table 3. Both *A. judaica* and *A. sieberi* exhibited similar degrees of growth inhibition with MIC-values of 78.12 to 312.5 mg/ml. The most sensitive strain was the Gram-positive *S. aureus* and *E. faecalis* (MIC: 156.25 mg/ml). The values of MBC or MFC were about 2x higher than that of MIC's (Table 3).

DISCUSSION

Medicinal plants have proven their pharmacological activities historically and nowadays still represent a valuable source of new drugs reaching the market (Atanasov et al., 2015; Che and Zhang, 2019). Due to their advantages for human health, researchers have long shown interest in phenolic and flavonoids agents in

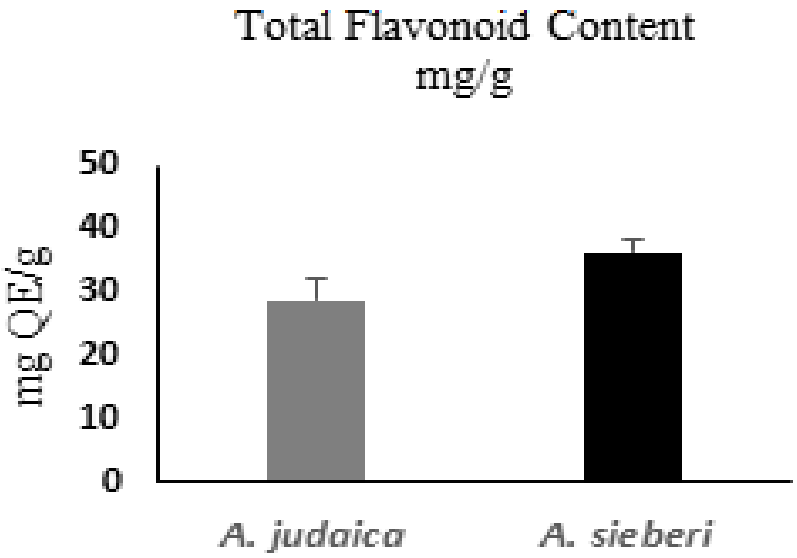

Figure 1. Total phenol and total flavonoid contents of *A. sieberi* and *A. judaica*.

Table 1. Scavenging activities of *A. judaica* and *A. sieberi* methanolic extracts.

Sample	(DPPH-radical scavenging activity in %)				
	10	50	100	500	1000
	(µg/mL)				
A. sieberi	8.6 ± 1.4	12.8 ± 2.8	27.8 ± 2.4	61.3 ± 2.9	73.6 ± 2.6
A. judaica	6.2 ± 3.7	10.8 ± 1.1	19.5 ± 1.0	47.4 ± 2.4	65.1 ± 3.9
Ascorbic acid	80.7 ± 2.0	85.1 ± 1.3	85 ± 1.2	88.7 ± 2.4	90.7 ± 1.4
	(ABTS radical cation scavenging activity in %)				
A. sieberi	6 ± 0.9	12.3 ± 2.9	21.9 ± 1.9	54.1 ± 2.4	71.3 ± 2.3
A. judaica	5.6 ± 0.6	9.3 ± 1.1	18.6 ± 1.1	43.9 ± 1.9	63.3 ± 2.1
Ascorbic acid	80.7 ± 2.4	81.2 ± 2.1	84.2 ± 1.9	87.2 ± 2.4	88.7 ± 2.1

In the columns, means ± SD with different letters notification are significant at ($P < 0.05$) (n = 3).

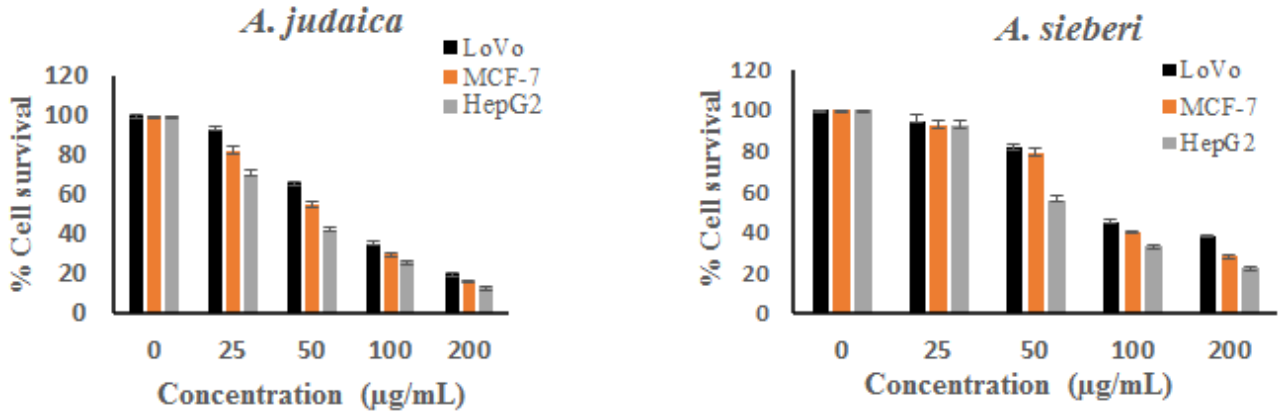

Figure 2. Cytotoxic effect of *A. judaica* and A. sieberi extracts on different cancer cells. Cells were seeded and treated as illustrated in method section. MTT assay was used to measure cell viability. Data represent the mean ± S.D of three independent experiments.

Table 2. IC50 values of *A. judaica* and *A. sieberi* methanolic extracts against different cancer cell lines.

Species	IC_{50} values (µg/ml)		
	MCF-7	LoVo	HepG2
A. judaica	58.4 ± 1.5	75.6 ± 1.6	42.8 ± 0.8
A. sieberi	86.2 ± 2	92.5 ± 2.8	62 ± 2.1
Doxorubicin	1.2 ± 0.2	0.95 ± 0.6	1.1 ± 0.3

Table 3. Minimal inhibitory concentrations, minimal bactericidal concentration (MBC) and minimal fungicidal concentration (MFC) of the crude extracts of *A. judaica* and *A. sieberi*.

	Activity	*S. aureus*	*E. faecalis*	*E. coli*	*P. vulgaris*	*Candida albicans*
A. judaica	MIC	156.25	156.25	625	312.5	78.12
	MBC	312.5	312.5	1250	625	NT
	MFC	NT	NT	NT	NT	156.25
A. sieberi	MIC	156.25	156.25	625	312.5	78.12
	MBC	312.5	312.5	1250	625	NT
	MFC	NT	NT	NT	NT	156.25
Gentamycin	MIC	7.8	7.8	3.9	3.9	NT
	MBC	15.6	15.6	7.8	7.8	NT
Nystatin	MIC	NT	NT	NT	NT	3.5
	MFC	NT	NT	NT	NT	7.0

S. aureus (ATCC 25923) and *E. faecalis* (ATCC 29212) and two gram-negative bacteria *E. coli* (ATCC 25922) and *P. vulgaris* (ATCC 8427) and one fungal strain *Candida albicans* (ATCC 60193). NT: not tested.

medicinal plants (Tungmunnithum et al., 2018). In this study, we reported that *A. judaica* and *A. sieberi* are considered as a promising source of phenolic and flavonoids compounds. Our findings are consistent with several studies that documented the presence of these constituents in same species grown in different regions of the world (Azimian and Roshandel, 2015; Bakr, 2015; Allam et al., 2019; Ranjbar et al., 2020).

The antioxidant capacity of phenolic and flavonoids compounds is well documented in several *in vitro* studies and they have been shown strong capacity of scavenging of several non-physiological radicals such as DPPH and ABTS ABTS (Pietta, 2000; Kosar et al., 2003; Payet et al., 2005; Cai et al., 2006; Kumar and Pandey, 2013). In this study, total phenols and flavonoids contents have been quantified from the aerial part of *A. judaica* and *A. sieberi*, which justifies the high antioxidant activity reported for the methanol extracts. It was noticed that extracts from both species exhibited a notable antioxidant activity in both DPPH and ABTS methods with *A. sieberi* demonstrating the highest activity than *A. judaica*. In a previous study, Al-Mustafa and and Al-Thunibat (2008) demonstrated that Jordanian *A. judaica* exhibited an antioxidant activity (DPPH-TEAC = 18.3 ± 0.6 mg g^{-1} and ABTS-IC_{50} = 104.6 ± 0.9) which is close to our findings. In addition, various species of *Artemsia* showed variation in their antioxidant capacity (Lopes-Lutz et al., 2008), which can be attributed to the quantity of phenolic compounds, including flavonoid, and climate and edaphic characteristics of the geographical areas.

Different forms of cancer are constantly gaining resistance to current drugs, creating a need for the discovery of new drugs. In this work, the methanol extracts of *A. sieberi* and *A. judaica* showed remarkable cytotoxic activity against all tested cancer cell lines. This could be due to the presence of artemisinin and other sesquiterpene lactones, which have been reported before for both species (Arab et al., 2006; Abbas et al., 2017). Artemisinin which is a sesquiterpene lactone demonstrated anticancer activity when tested *in vitro* and *in vivo* (Ferreira et al., 2010). Artemisinin was also found to be a good antibacterial, antifungal, antileishmanial, and antitumor agent (Appalasamy et al., 2014).

Due to pathogens developing resistance to existing drugs, millions of lives are lost every year owing to infectious diseases (Nicolaou et al., 2009; Yu et al., 2010). The ability of extracts to combat different species of microorganisms was explored. Assays involving *in vitro*

MIC methodologies are commonly used and provide data on the lowest concentration of an antimicrobial that inhibits the visible growth of a microorganism. The value of MIC is an accepted standard for measuring the sensitivity of microorganisms (e.g. bacteria in their planktonic phase) to inhibitors (Kalemba and Kunicka, 2003). Thus, the minimum inhibitory concentrations (MIC) of the *A. judaica* and *A. sieberi* extracts were tested to determine the antimicrobial effectiveness (Table 3). *Artemisia sieberi* was found to have similar activities of *A. judaica* against all microbes, except Gram–negative bacteria (*E. coli* and *P. vulgaris*), which were resistant against both plant species. The antibacterial activity of these species could be attributed to artemisinin, which had been tested on a wide range of bacteria (Appalasamy et al., 2014). Our results are in conformity with the study of Guetat et al. (2017) who reported that *A. sieberi* as well as *A. scoparia* and *A. judaica* possess high antibacterial activity.

Conclusion

Our results confirm the potential use of *A. judaica* and *A. sieberi* species in folk medicine and in primary health care. Our data support the antioxidant properties of these species which can interfere with oxidative stress and hence minimizing the risk of developing complex diseases. In addition, our results documented the anticancer properties of *A. judaica and A. sieberi* species suggesting the potential use of these species as a source of anticancer agents. The obtained results also provide a basis for a further investigation to characterize new compounds from these species that could be used as anticancer and antimicrobial agents. Further *in vitro* and *in vivo* investigation is still necessary to examine the reported bioactivity to confirm the beneficial uses of *Artemisia* species against cancer and infectious diseases.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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