Original Article

In-vitro Evaluation of Anti-microbial and Cytotoxic Activity of *Artemisia judaica* Leaves and Stem Extracts via Induction of Caspase Dependent Apoptosis

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ABSTRACT

Medicinal plants and herbs are commonly used in the world to treat various human disorders. *Artemisia judaica* is one of these herbal species that is commonly used in medicine due to its contents of many bioactive compounds such as; flavonoids, lactones, essential oil and sesqui-terpenoids. It was used in many traditional medicines as an anthelmintic, antispasmodic, anti-rheumatic, and antibacterial agent. In recent years, anti-bacterial and anti-cancer activity of medicinal herbs are highly investigated. The present study is focused on the anti-microbial and cytotoxic effect of methanolic extract of *Artemisia judaica* leaves and stem. The antimicrobial assay was done on different gram-positive and gram-negative bacteria and it was revealed that leaves and stem extracts possess high and moderate activity against *Staphylococcus aureus* (MIC 312.5μg/ml and 625μg/ml) and Proteus vulgaris (MIC 312.5μg/ml and 1250μg/ml) for leaves and stem, respectively. Extracts were screened against HepG2, HCT-116, MCF-7, A-549 and MRC-5 cancer cells and it was found that both extracts were active against all cell lines with highest selectivity and cytotoxic activity observed against HepG2 cells (IC_{50} = 3.38 and 6.84μg/ml, for leaves and stem respectively). Further mechanistic studies on HepG2 cells showed that both extracts resulted in S-phase arrest and induced apoptosis *via* activation of caspase-3, p53 and Bax

Key words: *Artemisia judaica*, Antimicrobial, Anticancer, Apoptosis, Mechanism.

INTRODUCTION

For thousands of years, plants have been used to treat various human diseases and hence they considered as important sources for many bioactive compounds. The use of natural products and supplements of medicinal herbs has been increased over the past three decades with more than 80% of people worldwide depend on them for some part of primary healthcare.[1]

Artemisia judaica is a perennial herb that is growing abundantly in North Africa and Middle Eastern countries,[2] As well in Saudi Arabia, Yemen and Egypt.[3-5] It has been used traditionally in the Egyptian medicine for the treatment of gastrointestinal diseases.[5] In addition; many Artemisia species have been used in Iranian traditional medicine as an anti-infectious, anti-bacterial, gastric tonic, digestive and stomachic.[6]

Major medicinal effects of Artemisia that have been reported include improved vision, cardiovascular health, capillary strength, connective tissue structure, and enhanced immune system functions, as well as decreased risk of atherosclerosis,

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cancer, arthritis and gastrointestinal disorders.[7,8] Also, it was found that its aqueous and ethanolic extracts possess anti-diabetic effect.[9]

It was found that Artemisia contains sesqui-terpene lactones and other active phytochemical components. Sesqui-terpene lactones were used for their therapeutic and other properties,[10] recently, monoterpenes, sesqui-terpenes, sesqui-terpene lactones, flavonoids, coumarins, sterols, poly-acetylenes have been isolated from Artemisia species.[11]

Isolated compounds from *Artemisia judaica* have exhibited antiviral, antibacterial, antifungal, and cyto-protective effects,[12-14] and used for the treatment of hepatitis, cancer and menstrual-related disorders,[15] *Artemisia judaica* showed a promising cytotoxic activity against some cancer cell lines,[16] which may be due to its essential oil content of thujone.[17]

The present study is designed to evaluate the anti-microbial and cytotoxic effect of methanolic extract of *Artemisia judaica* leaves and stem with mechanistic determination of its cytotoxic effect on different cell lines.

MATERIALS AND METHODS

Plant Collection and Extract Preparation

The aerial parts (Leaves and stem) of *Artemisia judaica*, were collected during the flowering stage from Hail region, KSA. Herbs were washed and shade dried for a week and was grinded to fine powder, then it was extracted with methanol at a ratio of 20 g dry powder in 200 ml of methanol for 48 hr using the maceration method. The liquid extract was filtered and concentrated under vacuum by using Soxhlet extraction and then stored in the dark at 4°C until use.

RESULTS AND DISCUSSION

Antimicrobial activity of *Artemisia judaica* stem and leaves methanolic extracts

We investigated the antimicrobial activity of *Artemisia judaica* against certain microbes, of which some have not been examined before for their susceptibility to *Artemisia judaica.*

Artemisia judaica methanolic extract was initially screened against Gram-positive bacteria (*S. aureus* and *B. subtilis*), Gram-negative bacteria (*E. coli* and *P. vulgaris*) and fungi (*A. fumigatus* and *C. albicans*) using a qualitative disc diffusion assay and results have been summarised in Table 1.

Results showed that the methanolic extract of leaves exerted moderate antimicrobial activity against most investigated microbes except for *P. vulgaris* and *S. aureus* whereby significantly high antimicrobial activity was exerted against these two microbes with inhibition zones of 16 mm and 15 mm, respectively. While methanolic extract of stem exerted weak antimicrobial activity against most investigated microbes except for *P. vulgaris* and *S. aureus* whereby significantly moderate antimicrobial activity was exerted against these two microbes with inhibition zones of 12 mm and 13 mm, respectively

Further quantitative analysis of leaves and stem extracts' antimicrobial activity was performed by investigating the minimum inhibitory concentration (MIC) against microbes using broth micro-dilution assay,[18] and the results were shown in Table 2. Results of the assay showed that both leaves and stem extracts possess good antimicrobial activity against *Staphylococcus aureus* followed by *Proteus vulgaris* with MIC values of 312.5µg/ml and 625µg/ml for leaves' extract and 312.5µg/ml and 1250µg/ml for stem extract, respectively.

Table 1: Antimicrobial activity of *Artemisia judaica* leaves and stem methanolic extract.

	Zone of inhibition diameter (mm)[a]					
	Gram-positive bacteria		Gram-negative bacteria		Fungi	
	S. aureus	*B. subtilis*	*E. coli*	*P. vulgaris*	*A. fumigatus*	*C. albicans*
Leaves' extract	15.2±1.4	7.8±0.6	14.1±1.3	15.9±1.54	NA[b]	11.7±1.15
Stem's extract	12.8±0.94	NA	7.5±0.91	11.6±0.6	NA	NA
Gentamycin	25.1±1.63	27.3±1.5	29.7±1.9	26.4±1.2	…….	…….
Ketoconazole	…….	…….	…….	…….	19.2±1.2	20.8±1.4

a Zone of inhibition diameters equal to 14mm and above were considered to indicate significant antimicrobial activity, 9mm–13mm were considered to indicate moderate activity, and less than 9mm were considered to indicate weak and insignificant activity. Zone of inhibition diameters were reported as mean (Zone of inhibition diameter ± SD) of three experiments.
b NA: No activity.

Table 2: Minimum inhibitory concentration (MIC) of *Artemisia judaica* leaves and stem' methanolic extract against selected bacteria and fungi.

	MIC (µg/ml)					
	Gram-positive bacteria		Gram-negative bacteria		Fungi	
	S. aureus	*B. subtilis*	*E. coli*	*P. vulgaris*	*A. fumigatus*	*C. albicans*
Leaves' extract	312.5	5000	625	312.5	NA	1250
Stem's extract	625	NA	10000	1250	NA	NA
Gentamycin	9.7	4.8	4.8	4.8	.....	.....
Ketoconazole	.....	.....	.....	.....	156.25	312.5

Table 3: IC_{50} values of *Artemisia judaica* leaves and stem methanolic extract against HepG2, HCT116, A549 and MCF-7 cancer cells.

	IC_{50} (µg/ml)[a]			
	HepG2	HCT116	A549	MCF-7
Leaves extract	3.38 ± 0.12	7.06 ± 0.65	7.64 ± 0.82	7.55 ± 0.91
Stem extract	6.84 ± 0.69	12.8 ± 1.4	27.2 ± 2.4	30.3 ± 2.6
Vinblastine sulphate	0.88 ± 0.24	1.45 ± 0.31	7.07± 0.39	2.05 ± 0.37

a IC_{50} values are reported as the mean (IC_{50}±*SD) of three experiments*.

Table 4: IC_{50} values of *Artemisia judaica* leaves and stem methanolic extract against MRC-5 normal cells.

	IC_{50} (µg/ml)[a]	Selectivity index (SI)[b]			
	MRC-5	HepG2	HCT116	A549	MCF-7
Leaves extract	26.6 ± 2.3µg/ml	7.87	3.77	3.48	3.66
Stem extract	61.1 ± 5.2µg/ml	8.93	4.77	2.24	2.02

a IC_{50} values are reported as the mean (IC_{50}±*SD) of three experiments. B SI = (IC_{50}* of MRC5)/(IC_{50} of cancer cell).

Cytotoxic activity of *Artemisia judaica* leaves and stem methanolic extract against cancer cell lines

Artemisia judaica methanolic extract decreased cancer cell viability and demonstrated selectivity towards them

The anticancer potential of *Artemisia judaica* was not investigated on variable cancer cell lines, therefore we decided to examine cytotoxic activity of methanolic extract of aerial parts (leaves and stem) of *Artemisia judaica* on different types of cancer cell lines and elucidate its mode of action

The methanolic extract of *Artemisia judaica* leaves and stem has been screened against HepG2, A549, HCT116 and MCF-7 cancer cell lines and the resulting IC_{50} values have been summarised in Table 3. Results have shown that the leaves extract exerted high cytotoxic activity across all cell lines with IC_{50} values close to that of vinblastine sulphate in case of HepG2 and A549 cell lines, while stem methanolic extract exerted high cytotoxic activity against HepG2, moderate cytotoxic activity against HCT116 cell lines and weak cytotoxic activity against A549 and MCF-7 cell lines

The highest cytotoxic activity was exerted by leaves extract against HepG2 cells with an IC_{50} value of 3.38µg/ml. It is also interesting to note that the leaves extract possessed cytotoxic activity similar to that of vinblastine sulphate on A549 cell lines with IC_{50} value of 7.64µg/ml and 7.07µg/ml, respectively.

The leaves and stem extracts showed more selectivity towards all cancer cell lines relative to normal, healthy MRC5 cells, with highest selectivity being demonstrated against HepG2 cells as shown in Table 4.

This high selectivity indicates that the leaves and stem extracts are expected to be less toxic towards healthy cells. These interesting results in general, and against HepG2 cells specifically, encouraged us to further investigate the mechanism of action of both leaves and stem extracts in HepG2 cancer cells.

Artemisia judaica methanolic extract induced S-phase cell-cycle arrest in HepG2 cells

The highest cytotoxic activity for the methanolic extract was demonstrated against HepG2 cells, so we wanted to further characterise the extract's bioactivity *via* investigating its effect on cell-cycle progression.

HepG2 cells treated with the methanolic extract of leaves and stem showed an increase in the fraction of cells in the S-phase (56.02% and 54.08 % compared to 47.13% in the untreated cells), respectively as shown in Figure 1.

Moreover, a significant increase in the fraction of cells in the pre-G1 phase was also observed after treatment with leaves and stem extracts (32.92 % and 29.59 % compared to 2.37 % in the untreated cells) which indicates that both leaves and stem extracts induce apoptosis in HepG2 cells. Therefore, cell-cycle analysis

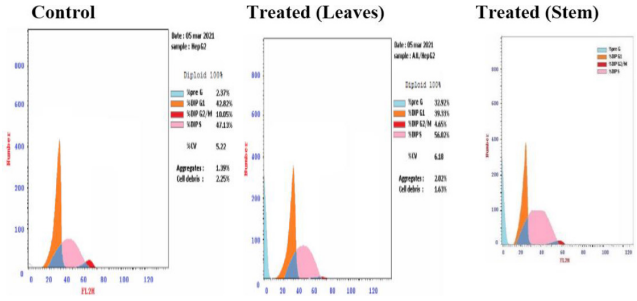

Figure 1: Representative cell-cycle histograms showing the effect of *Artemisia judaica* methanolic extracts on cell-cycle progression in HepG2 cells after 72 hr of treatment at IC_{50} concentration.

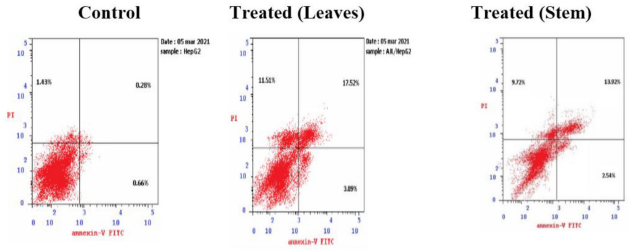

Figure 2: Representative Apoptosis quadrant plots illustrating the apoptotic effects of *Artemisia judaica* methanolic extracts on HepG2 cells. The cells were treated with the extract at IC_{50} concentration for 72 hr.

revealed that the extract induced S-phase arrest and apoptosis in HepG2 cells.

Artemisia judaica leaves and stem methanolic extracts induced caspase-dependent and p53-mediated apoptosis in HepG2 cells

Cell-cycle analysis indicated that the leaves and stem extracts induced apoptosis in HepG2 cells. Therefore, to further investigate the induction of apoptosis by the extract, an Annex in V/pro-podium iodide (PI) apoptosis assay was conducted whereby HepG2 cells were treated with leaves and stem extracts. Results of the assay showed that both extracts induced early (3.89 % and 2.54 %, respectively compared to 0.66 % in the untreated cells) and late (17.52 % and 13.92 %, respectively compared to 0.28 % in the untreated cells) as shown in Figure 2. Moreover, there was also an increase in the number of necrotic cells after treatment (11.51 % and 9.72 %, respectively compared to 1.43 % in the untreated cells).

Therefore, it can be deduced from the apoptosis assay that the extract resulted in cancer cell death mostly *via* the induction of apoptosis while a less percentage of cells were found to have undergone necrosis.

The induction of apoptosis by leaves and stem methanolic extracts were further confirmed *via* investigating the expression levels of apoptosis-related proteins, such as

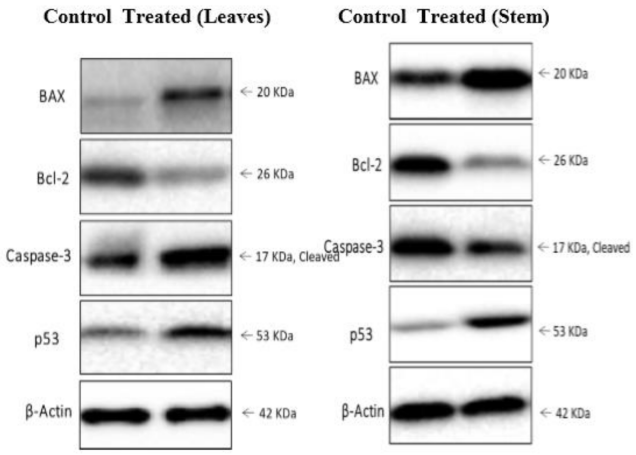

Figure 3: Western blot analysis of cleaved caspase-3, p 53, Bax and Bcl-2 in HepG2 cells. Cells were treated with *Artemisia judaica* methanolic extracts for 72 hr at IC_{50} concentration. β actin was used as an internal control.

caspase-3 and p53. Activation of caspases is considered to be a hallmark of apoptosis, especially caspase-3 which is regarded as the most important executioner caspase.[19] p 53 is a tumour suppressor protein that mediates several anti-proliferative processes including apoptosis, and its activation is crucial for suppressing tumorigenesis.[20] Western blot analysis showed an increase in the protein expression levels of cleaved caspase-3 after treating HepG2 cells with leaves methanolic extract, while no increase was observed after treating HepG2 cells with stem methanolic extract. This indicates the induction of apoptosis in the cancer cells upon treatment with leaves extract and corroborates the data obtained from the Annexin V/PI assay as shown in Figure 3.

Moreover, p 53 expression levels were found to be enhanced following treatment with the methanolic extracts of both leaves and stem which might indicate that the induced apoptosis is probably mediated *via* p53. Therefore, *Artemisia judaica* leaves methanolic extract was found to cause cell death *via* activating caspase-3 and p53 in HepG2 cells, while stem extract was found to cause cell death *via* activating only p53 in HepG2 cells.

Bax is a pro-apoptotic protein that is a primary target of p53 and is responsible for caspase activation during apoptosis, however, the pro-apoptotic effects of Bax are suppressed by the anti-apoptotic protein Bcl-2.[21,22] Therefore, investigating these proteins is supposed to provide further insight into the apoptosis mechanism triggered by leaves and stem extracts. Western blot analysis revealed that the methanolic extracts of leaves and stem increased the protein expression level of Bax but reduced the expression level of Bcl-2 in HepG2 cells as shown in Figure 3. This confirmed the pro-apoptotic

effect of both extracts and corroborates the results of the other apoptosis-related assays

In summary, leaves extract induced apoptosis *via* modulation of p53, caspase-3 and Bax/ Bcl-2, while that of stem-induced apoptosis *via* modulation of p53 and Bax/Bcl-2 only.

CONCLUSION

The current research involved assessing the antimicrobial and cytotoxic activity of *Artemisia judaica* leaves and stem methanolic extracts in greater details. The extracts were found to possess good antimicrobial activity against *Staphylococcus aureus* and *Proteus vulgaris*. Moreover, the extracts exerted their highest cytotoxic activity against HepG2 cells and were found to possess high selectivity against these cells. Further studies showed that the extracts caused caspase-dependent, p 53-mediated apoptosis in HepG2 cells and resulted in S-phase cell cycle arrest. This study demonstrated the antimicrobial and anticancer potential of *Artemisia judaica* methanolic extracts and provided a better understanding about extracts' anticancer mode of action.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

ABBREVIATIONS

MIC: Minimum Inhibitory Concentration; **HepG2:** Human Liver Cancer Cell Line; **HCT-116:** Human Colorectal Carcinoma Cell Line; **MCF-7:** Breast Cancer Cell Line; **A-549:** Adenocarcinomic Human Alveolar Basal Epithelial Cells; **MRC-5:** Medical Research Council Cell Strain 5 which is diploid cell line; **IC_{50}:** Half-Maximal Inhibitory Concentration; **p53:** Tumour suppressor protein; **Bax:** Apoptosis Regulator Protein; **S-Phase:** Synthesis Phase

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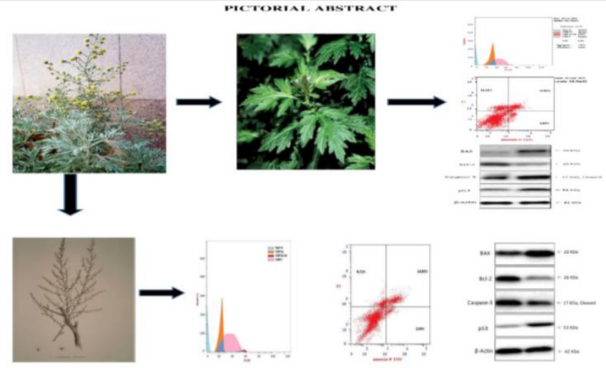
PICTORIAL ABSTRACT



SUMMARY

Methanolic extracts of *Artemisia judaica* leaves and stem were screened for their antimicrobial and cytotoxic activities and it was found that they possess good antimicrobial activity against *Staphyllcoccus aureus* and *Proteus vulgaris*, while they possess high cytotoxic activity against HepG2 cells by caspase-dependent, p 53-mediated apoptosis mechanism.

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