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Antifungal effect of *Echinophora platyloba* on expression of CDR1 and CDR2 genes in fluconazole-resistant *Candida albicans*

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ABSTRACT

Background: Several studies examined the effect of the *Echinophora platyloba* extract in treatment of azole-resistant *Candida albicans* clinical isolates.

Objective: We investigated the effect of *E. platyloba* extract on expression of CDR1 and CDR2 genes in fluconazole-resistant clinical isolates of *C. albicans* using real-time PCR.

Materials and Methods: The crude extract of *E. platyloba* was obtained using percolation method. Using serial dilution method, different concentrations of extract were achieved. Two hundred microlitres of fungal suspension (10^6 CFU/ml) was added to the media and cultured with different concentrations and then incubated at 37 °C for 48 h. The concentration of extract in the first tube, which inhibited the growth of *C. albicans*, was recorded as the Minimal Inhibitory Concentration (MIC). In order to analyse the expression of CDR1 and CDR2 genes, RNA was extracted from *C. albicans* isolates before and after treatment with MIC of *E. platyloba* using glass beads and the denaturing buffer agents in an RNase-free environment and then the cDNA was synthesised and used for real-time PCR assay.

Results: Twenty of total of 148 isolates were resistant to fluconazole. The MIC and MFC for the alcoholic extract of *E. Platyloba* were 64 mg/ml and 128 mg/ml, respectively. Real-time PCR results revealed that the mRNA levels of CDR1 and CDR2 genes significantly declined after incubation with *E. Platyloba* (both p values < 0.001).

Conclusion: *E. Platyloba* is effective in reducing CDR1 and CDR2 expression which in turn plays an important role in fluconazole resistance in *Candida* species.

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Real-time PCR; Echinophora platyloba; fluconazole-resistant; Candida albicans

Introduction

The incidence of fungal infections has been steadily increasing in the past decade as a result of the increase in the number of immunocompromised patients and prolonged antibiotic therapy.[1] Candidiasis is the most common fungal infection among AIDS patients; oral and oesophageal Candidiasis occurs in more than 70% of patients.[2] Vaginal candidiasis is a common mucosal infection caused by the opportunistic yeast *Candida albicans*, with the highest prevalence among women aged 20–30 years.[3] In addition to these facts, a recent study revealed that *Candida* can increase chance for the onset of diabetes by provoking an elevated level of insulin secretion.[4]

Among the different antifungals available, the fungistatic azoles are widely used for the treatment of *Candida* infections. The emergence of azole-resistant *C. albicans* strains has been associated with the widespread and prolonged use of azoles, especially fluconazole, in treatment of vulvovaginal candidiasis which frequently fails.[5,6] A common mechanism of resistance to fluconazole in *C. albicans* is failure of cells to accumulate the drug due to enhanced expression of certain proteins encoded by CDR1 and CDR2 genes. The CDR1 and CDR2 genes encode proteins which belong to the superfamily of ATP-binding cassette transporter.[7,8] Overexpression of these transporters plays an important role in fluconazole resistance in *C. albicans*, due to increased fluconazole efflux.[9] Several studies demonstrated enhanced susceptibility to the drug as a result of disruption in CDR1 and CDR2 in *C. albicans*.[8,10]

In recent years, the use of herbal products and herbal supplements has dramatically increased all around the world, including in the United States and the United Kingdom.[11,12] Moreover, microbiologists have been interested in the study of plant products as antimicrobial and antifungal agents.[13]

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Echinophora platyloba DC belongs to the Apiaceae or Umbelliferae family, and grows exclusively in the west and north-west of Iran. *E. platyloba* is a pasture plant and is mainly used for food flavouring and preserving in some provinces of Iran.[14] Several studies tried to examine the effect of the *E. platyloba* extract, alone or in combination with fluconazole, in the treatment of azole-resistant *C. albicans* clinical isolates.[14–19] These findings support the theory that *E. platyloba* may reduce the expression of genes which play an important role in fluconazole resistance in *C. albicans*.

In the present study, real-time PCR was utilised to form a hypothesis on the effect of *E. platyloba* extract on the expression of CDR1 and CDR2 genes in fluconazole-resistant clinical isolates of *C. albicans* from patients with recurrent vulvovaginal candidiasis.

Materials and Methods

Microorganisms and media

A total of 148 *C. albicans* clinical isolates were collected, between August and December 2014, from the vagina of women with recurrent vaginal candidiasis in AJA Hospital, Tehran, Iran. The clinical isolates were tested for susceptibility to fluconazole using the disc diffusion method as described in Clinical and Laboratory Standards Institute (CLSI), document M44-A.[20] We used *C. albicans* strain ATCC10231, purchased from the Biotechnology Institute of the Iranian Research Organization for Science and Technology, Tehran, Iran, as control. Twenty (13.5%) isolates were resistant to fluconazole and were included in further evaluations. The isolates were grown at 37 °C on Sabouraud dextrose agar with chloramphenicol medium (Biolife Italiana Srl, Milan, Italy) and stored at 4 °C. Stored isolates were passaged on fresh media to obtain colonies for further evaluations.

Preparation of plant extract

The flowering aerial parts (leaves and flowers) of *E. platyloba* were harvested from west of Iran (Aligoodarz district) in October 2014. The harvested materials were shade-dried at ambient temperature (about 25 °C) and air circulation for 1 week. The air-dried materials were mixed and ground to obtain a homogeneous fine-grade powder. The crude extract was obtained using percolation method. One-hundred grams of powdered sample was soaked in 500 ml of pure ethanol (analytical grade; Merck Millipore Corporation, Darmstadt, Germany) and frequently agitated for 3 days. The mixture was filtered using a Whatman number 4 filter paper and the crude extract was collected. Using a water bath, the crude extract was distilled at 50 °C and then dried in an oven at 37 °C. Finally, ethanolic solution of the *E. platyloba* extract was made with known concentration and used for further investigation.

Antifungal activity of plants extract

Serial dilutions of the extract were made in serial tubes to achieve the following range of extract concentration 512, 256, 128, 64, 32, 16, 8, 4, 2 and 1 mg/ml, respectively. Two hundred microlitres (µL) of *C. albicans* fungal suspension (10^6 CFU/ml) was added to the Sabouraud dextrose agar with chloramphenicol medium and cultured with different concentrations of the *E. platyloba* extract and then incubated at 37 °C for 48 h. The 11th tube was made without any extract (media growth control) and the 12th tube without a fungal suspension (control for contamination). The concentration of extract in the first tube, which inhibited the growth of *C. albicans*, was recorded as the Minimal Inhibitory Concentration (MIC).

In order to treat the *C. albicans* strains with *E. platyloba* extract, 200 µL of 10^6 CFU/ml suspensions of *C. albicans* were added to 100 µL of MIC of plant extract in a sterile 96-well microplate and then incubated at 37 °C. After 24 h, using a sterile loop, treated strains were cultured on chloramphenicol Sabouraud dextrose agar medium and used for future analysis of gene expression.

RNA extraction and real-time PCR

To compare the changes in the expression of CDR1 and CDR2 genes, RNA was extracted from *C. albicans* isolates before and after treatment with MIC of *E. platyloba* using glass beads and the denaturing buffer agents in an RNase-free environment.[15] To prevent contamination with genomic DNA, RNA extracts were treated with 1Unit of DNaseI (Fermentas, Thermo Fisher Scientific Inc., Germany) per 10 µl of RNA at 37 °C for 1 h. Five microlitres of the RNA was separated using 2% agarose gel electrophoresis and then visualised and photographed with an Image Master® Video Documentation System to check the quality of RNA extracts. The cDNA was synthesised using a two-step RT-PCR kit (Vivantis, Malaysia) following manufacturer's instructions. Synthesised cDNA samples then were stored at –20 °C and directly used in real-time PCR assay. The housekeeping gene ACT1 was used as a normalising gene. The PCR primers sequence used to amplify and identify the *C. albicans* CDR1, CDR2 and ACT1 genes are shown in Table 1.

We used SYBR® Green I (Fermentas, Thermo Fisher Scientific Inc., Germany), a specific DNA-binding dye, to detect amplification of the genes. The cycling conditions were 35 cycles of denaturation at 95 °C for 5 min, followed by annealing for 30 s at 65 °C for ACT1 and at 55 °C for CDR1 and CDR2, and then elongation at 72 °C for 10 s, followed by termination in a final cooling step for 30s at 72 °C. Threshold cycle (Ct) is defined as the number of cycles required for the fluorescent signal to cross the threshold (i.e. exceeds background level). It is a relative measure of the concentration of target in the PCR reaction.

Table 1. Primer sequences of genes used for real-time PCR in this study.

Primer	Sequence
CDR1	Forward: 5′-TGTGTACTATCCATCAACCATCAGC-3′ Reverse: 5′-CACCAAAATAAGCCGTTCTACCA-3′
CDR2	Forward: 5′-TGGCAAACAATCCAACAATACA-3′ Reverse: 5′-AATCAAGGGAATAGATGGGTCA-3′
ACT1	Forward: 5′-CCAGCTTTCTACGTTTCC-3′ Reverse: 5′-CTGTAACCACGTTCAGAC-3′

Table 2. Minimum inhibitory concentrations (MIC) and minimum fungicidal concentrations (MFC) of E. platyloba extract.

	MIC (mg/ml)	MFC (mg/ml)
Standard strain ATCC10231 *Candida albicans*	32	64
Clinical isolates of *Candida albicans*	64	128

The expression levels of CDR1 and CDR2 were evaluated using the 2–ΔΔCt method, where the Ct was the average threshold cycle number from three independent experiments.[16] Data were presented as the fold change in gene expression normalised to the 18SrRNA gene as control.

Statistical analyses

Statistical analyses were performed using statistical package for social sciences (SPSS), version 18.0 release for Microsoft Windows (SPSS Inc, Chicago, Illinois). In all tests, a *p* value of less than 0.05 was considered statistically significant. The mean of the Ct of CDR1 and CDR2 genes before and after treatment with *E. platyloba* are expressed as mean ± standard deviation. The levels of ΔCt of the CDR1 and CDR2 genes before and after incubation with plant extract were compared using paired *t* test, separately.

Results

Twenty (13.6%) out of a total of 148 *C. albicans* isolates from women with recurrent *Candida* vaginitis were resistant to fluconazole. To assess the antifungal effect of plants, *C. albicans* isolates suspension was added to different concentrations of *E. platyloba* extract. Results of serial dilution method showed the MIC of 64 mg/ml of ethanolic extract of *E. platyloba* on *C. albicans* clinical isolates. There was an overt growth of yeast in the control tube (10th tube). The minimum fungicidal concentration (MFC) of ethanolic extract of *E. platyloba* was 128 mg/ml. MIC and MFC of the *E. platyloba* in clinical isolates and reference strain ATCC10231 are shown in Table 2.

After incubation of clinical isolates of *C. albicans* with 64 mg/ml of *E. platyloba* extracts in microplate for 24 h at 37 °C, clinical isolates were cultured on Sabouraud dextrose agar with chloramphenicol for 48 h at 37 °C. Total RNA before and after treatment was extracted, and the expression of CDR1 and CDR2 genes was evaluated using real-time PCR. There were no primer dimers or non-specific amplification products according to the melting curves and melting peaks of the two tested genes. A single band of PCR product with the expected length on agarose gel electrophoresis also confirmed the specificity of the PCR reactions (data not shown). Using the 2–ΔΔCt method, the expression of CDR1 and CDR2 genes was compared before and after treatment with *E. platyloba*. Results of paired *t* test revealed that exposure to *E. platyloba* significantly increased the ΔCt of CDR1 and CDR2 genes (*p* values < 0.001 for both tests) which shows the decline in mRNA levels of both genes (Table 3).

Discussion

Emersion of resistance of microorganisms to the antimicrobial agents has been rapidly increasing; but the rate of new antimicrobial production is insufficient to rectify our needs. This shows the importance of investigation on development of new promising antimicrobial agents or to guarantee the future of antimicrobial therapy.[21] The goal of this study was to investigate the effect of E. *platyloba* extract on expression of CDR1 and CDR2 genes in fluconazole-resistant clinical isolates of *C. albicans* using real-time PCR. Clinical isolates were gathered from women with recurrent vulvovaginal candidiasis. The fluconazole resistance of the clinical isolates was proofed using disc diffusion method according to the method introduced by CLSI, document M44-A.[20]

Azole resistance in *Candida* species is the most prevalent type of resistance to antimycotics, which is an important cause of treatment failure in vulvovaginal candidiasis.[22,23] In our study, the prevalence of fluconazole resistance in clinical isolates was 13.6% which is comparable to previous report by Sojakova et al. [24] in Slovenia (12.8%). In an investigation of paediatric Iranian patients by Teymouri et al. [25], 5.2% of isolates were fluconazole-resistant.

Studies confirmed that the nature of azole resistance is multifactorial, with a predominance of overexpression of genes encoding drug efflux pumps.[26] Overexpression of the MDR1, CDR1 and CDR2 genes, encoding major

Table 3. Comparison of the levels of ΔCt of the CDR1 and CDR2 before and after incubation with E. platyloba extract.

	ΔCt before incubation	ΔCt after incubation	
Gene	(mean ± standard deviation)	(mean ± standard deviation)	*p* value
CDR1	20.6 ± 0.5	29.2 ± 1.4	<0.001
CDR2	21.1 ± 1.1	26.1 ± 1.2	0.004

drug efflux pumps using the proton motive force and ATP to transport drugs across the plasma membrane, results in failure of cells to accumulate antifungals.[27,28]

Genus *Echinophora* has 10 different species and belongs to the family Apiaceae or Umbelliferae.[29] Species *E. platyloba* is native to Iran and is mainly represented in the flora of the west and north-west regions of Iran. Based on the specific properties of this plant as a food preserver, several studies were performed to examine the antimicrobial and antifungal effects of *E. platyloba* extract.[16,19,30,31] The results of our study also demonstrated antifungal activity of *E. platyloba* extract (MIC of 64 mg/ml and MFC of 128 mg/ml). Studies on the chemical compositions of *E. platyloba* showed this plant contains saponin, alkaloid and flavonoid.[32,33] Previous studies demonstrated the fungicide potential of saponins, CAY-1, a steroidal saponin, has shown to be a potent fungicidal agent by disrupting the membrane integrity of the *C. albicans* cells.[34] Additionally, the antifungal effect of alkaloid agents has been shown in another study.[35] These findings suggest that the antimicrobial and antifungal effect of *E. platyloba* may be related to these components.

Avijgan et al. [14] recently showed that combination therapy with *E. platyloba* and Amphotericin is effective in treatment of *C. albicans* isolated from women suffering chronic recurrent vaginitis. The synergic antifungal activity of mixture of *E. platyloba* extract and antifungal drugs suggest the hypothesis that the plant may play a role in reducing the drug resistance in *C. albicans* isolates. Evaluating the expression of genes which are responsible in drug resistance in *Candida* species is the most accurate way to prove this hypothesis.

Our findings revealed that the mRNA levels of *CDR1* and *CDR2* of fluconazole-resistant *C. albicans* significantly decreased after incubation with MIC (64 mg/ml) of ethanolic extract of *E. platyloba*. Aslani et al. [36] also evaluated the expression of ERG11 and MDR1 genes in fluconazole-resistant clinical isolates of *C. albicans* after incubation with ethanolic extract of *E. platyloba*. Using real-time PCR, they reported that the expression of *ERG11* significantly decreased after treatment of isolates with *E. platyloba* extract, while there was no significant change in mRNA levels of *MDR1*.

In conclusion, *E. platyloba* has direct *in vitro* anti-*Candida* effects and also the plant extract reduces mRNA levels of *CDR1* and *CDR2*, two important genes which play a role in resistance to azole drugs in *C. albicans*. Future studies on the effect of *E. platyloba* extract on other genes that are responsible for azole resistance in *Candida* isolates are suggested. Also, we suggest *in vivo* trials to investigate the effect of these plants in curing patients with azole-resistant vaginal candidiasis. This work represents an advance in biomedical science because it shows that *E. platyloba* extracts can overcome fluconazole resistance in *C. albicans* by reducing the expression of *CDR1* and *CDR2*.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Summary Table

What is known about this subject:

- The incidence of fungal infections has been steadily increasing in the past decade.
- The emergence of azole-resistant *C. albicans* strains has been associated with the widespread and prolonged use of azoles.
- Overexpression of *CDR1* and *CDR2* plays an important role in fluconazole resistance in *C. albicans.*

What this paper adds:

- Exposure to *E. platyloba* extracts significantly increases the ΔCt of *CDR1*.
- Exposure to *E. platyloba* extracts significantly increases the ΔCt of *CDR2*.
- *E. platyloba* extracts declines the mRNA levels of both genes and can reduce fluconazole resistance in *C. albicans*.