In Vitro Anti-Candidial Activity of Some Iranian Medicinal Plants Against Candida Species

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Abstract

Background: Candida albicans is an organism most often associated with serious fungal infection, which has recently shown an increased resistance to commercial antifungal agents. As a result, using medicinal plants as an alternative method to address health problems has received a particular attention in developing countries.

Objective: This study aimed to examine the anti-Candidial potential of the extracts from Zataria multiflora Boiss (ZMB), Stachys acerosa Boiss (SAB), Prangos ferulacea (L.) Lindl (PFL), Tanacetum parthenium L. (TAPL), Teucrium polium L. (TEPL), and Cinnamomum zeylanicum L. (CZL) against three strains of Candida, including C. albicans, C. glabrata, and C. tropicalis.

Materials and Methods: To this end, several tests were performed to determine the minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC) against Candida species, using the agar well diffusion method (AWDM).

Results: According to our study results, the hydroethanolic extracts of six medicinal plants exhibited anti-Candidial activities. The extracts of ZMB, SAB, and CZL demonstrated strong anti-Candidial activities, while the hydroethanolic extracts of PFL, TAPL, and TEPL revealed moderate anti-Candidial activities at any of the tested concentrations. The highest inhibitory activity (ZOI: 38 mm) was recorded for the effect of CZL on C. albicans with MIC = 1.56 mg/mL, and the lowest anti-Candidal one (ZOI: 8 mm) was documented for the effect of T. parthenium on C. albicans with minimum inhibitory concentration (MIC) = 50 mg/mL.

Conclusion: The ascending sequence of fungicidal growth inhibition zones was as follows: C. zeylanicum > Z. multiflora > S. acerosa > T. polium > T. parthenium and P. ferulacea.

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Background

Due to the abuse of antibiotics and in an attempt to develop safe drugs, antimicrobial properties of medicinal plants have recently gained greater research attention. Nearly 150 species of Candida have been identified, out of which C. albicans is one of the most pathogenic species causing candidiasis.1 Candida albicans is commonly seen with serious fungal infections and has often been shown to resist the commercial antifungal drugs.2 Moreover, non-Candida albicans species including C. glabrata, C. guilliermondii, C. parapsilosis, and other species have become resistant to common antifungal drugs.3,5 Due to the development of pathogenic fungi resistance to existing antibiotics, the emergence of new pathogenic fungi, as well as the existence of immunocompromised patients, therefore, it is necessary to identify novel antifungal agents obtained from plants in nature.6 One of the largest genera of Lamiaceae family is the genus Stachys acerosa Boiss. Thirty-four of species of Stachys acerosa have been identified in Iran, 13 of which are endemic.7 Stachys is popularly called Sonboleh Kosary in Persian.8 Various species of Stachys are known as medicinal plants in the folk medicine of Iran and Turkey.9 Several studies have reported the biological properties of Stachys species, including antimicrobial,8,10 antioxidant,11 and anti-inflammatory properties.12 Moshafi et al, for example, investigated the components and antibacterial properties of this plant and identified carvacrol and caryophyllene oxide as the most important constituents of the plant, whose antibacterial effects had been previously reported by other studies.13 In Iranian folk medicine, Stachys inflata Benth is used for dealing with infection, asthma, rheumatic, and inflammatory disorders.14 Zataria multiflora Boiss. belongs to the Labiatae family that is distributed only in the southern and central parts of Iran, Pakistan, and Afghanistan. Z. multiflora is used as medicinal plants for condimental purpose in these countries. The native name of Z. multiflora in Iran is...
Avishan Shirazi that has conventional applications such as antispasmodic antiseptic and anesthetic. The most essential constituents in oil from this plant contain various levels of thymol, carvacrol, and phenolic derivations with strong antimicrobial properties. Antimicrobial properties of this plant have been previously studied. Prangos ferulaecea (L.) belongs to Apiaceae; it is native to Iran but is known as Jashir1 and has significant pharmaceutical, nutritional, and antioxidant properties. Strong anti-fungal and antibacterial properties of this plant against several microorganisms have been also reported previously. P. feruleaceae is native to Eastern Europe but now is also found in the Middle East and Central Asia. It is an important herb that reaches 150 cm in length, and its leaves are used as animal fodder due to their special biological properties and its fruits and roots are used for medicinal purposes. The main essential oil components of P. ferulaecea, such as monoterpane hydrocarbons, have been discussed in reviews of literature from several studies. According to these studies, the most important components of this plant are γ-terpinene, α-and β-pinene, δ-3-carene, and β-phellandrene. Cinnamomum zeylanicum (L.) belongs to Lauraceae family, commonly known as cinnamon, is native to Indonesia. A previous study has already documented the biological activities of C. zeylanicum such as parasiticidal, anti-spasmodic, insecticide, antiseptic, as well as being analgesic and astringent activities. The component of cinnamaldehyde is rich in C. zeylanicum bark essential oil. Furthermore, β-caryophyllene, 1,8 cineole, linalool, cinnamyl acetate, eugenol, and other terpenes are present in this plant. Cinnamon is used as a spice in cooking, a seasoning and flavoring ingredient in confectionery, a substance in treating colds and diarrhea, as well as an antioxidant. Cinnamon has also been recognized for its antifungal activity and antimicrobial properties, and its essential oil is used as a food preservative. Previous studies have shown that C. zeylanicum bark has significant medicinal properties useful in dealing with type II diabetes and insulin resistance. Tanacetum parthenium L., locally called feverfew, as well as the Asteraceae family have been used for treating inflammation and migraine, and their effects on migraine have been investigated by several clinical studies. T. parthenium is known as a wild plant in the provinces of Azarbaijan, Tehran, Hamedan, Mazandaran, Golestan, Gilan, and Yazd, which is also found in North, West, East, and center of Iran. According to the previous studies, the important component of the essential oil from this plant is camphor. Moreover, a study by Izadi et al has found that the antifungal effect of T. parthenium essential oil is extremely strong, even stronger than the antibacterial effect, all due to its compounds such as camphor, chrysanthenyl acetate, and camphene. Another study has also reported that the strong antibacterial effect of T. parthenium is due to the high amounts of flavonoids, parthenolides, sesquiterpenes, lactones, other terpenoids and phenolic compounds in the given plant. The genus Teucrium polium belongs to the family of Lamiaceae. T. polium locally called “Kalpooreh”, and is considered as an important traditional medicinal plant in Khuzestan, South, and west of Iran. Previous studies have revealed that T. polium is rich in compounds such as flavonoids, tannins, and alkaloids. The leaves and flowering tops of T. polium have antiseptic, anti-inflammatory, antioxidant, antifungal, and antibacterial properties. Given the above discussion, this study aimed to examine the anti-fungal properties of the mentioned medicinal plants against candida species including C. albicans, C. glabrata, and C. tropicalis. Due to the increasing resistance of microorganisms to the antibiotics, the present study also aimed to draw people and practitioners’ attention to using natural antimicrobial compounds in the plants as an alternative method for taking chemical medicines.

Materials and Methods
Medicinal Plants
The fresh leaves of Zataria multiflora Boiss (ZMB), Stachys acerosa Boiss (SAB), Prangos ferulaecea (L.) Lindl (PFL), Tanacetum parthenium L. (TAPL), Teucrium polium L. (TEPL), and Cinnamomum zeylanicum L. (CZL) were prepared from the Center for Agriculture and Natural Resources (ANRC) Ahvaz, Iran; and the stem of CZL was purchased from a local market. Botanical names, voucher specimen, as well as the data on traditional use and parts of the studied plants are presented in Table 1. Voucher specimens were deposited at the herbarium at the ANRC and identified by the third author (S.Y.N).

Preparation of Extracts
The stems and leaves of the selected medicinal plants were dried in the shade and crushed into fine powder. The dried plant material (10 g) was soaked in 100 mL of 85% ethanol in a glass beaker and then kept in a rotating shaker for 72 hours. Then the suspension was filtered using Whatman No. 1 filter paper. The purified ethanolic extracts were dried at room temperature to evaporate the alcohol. The dried extracts were stored in sterile bottles at -20°C until next use.

Fungal Isolates and Fungal Suspensions Preparation
A total of three Candida isolates, including C. albicans, C. glabrata, and C. tropicalis were obtained from patients with periodontitis and gingivitis referring to the educational clinics of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. These specimens were recognized based on colony color on CHROMagar Candida medium (CHROMagar, France). Phenotypic recognition included germ tube formation at 37°C in bovine serum, the formation of chlamydoconidia on corn
meal agar medium (Merck, Germany) plus 1% Tween 80, and recognition of C. albicans growth at 45°C carried out according to the procedure presented in the previous study.31 Stoke fungal strains were cultured on Sabouraud Dextrose Agar (SDA; Merck, Germany) and then diluted in normal sterile saline solution (0.9%) in order to obtain 5 x 10^5 CFU/mL, adjusted with 0.5 McFarland turbidity.32

**Determination of Anti-Candidial Activity**

Anti-fungal activities of the selected hydroethanolic extracts were assayed using agar well diffusion method (AWDM) according to the procedure followed in a previous survey30 after making minor amendments to it. Aliquots 2 mL pure dimethyl sulfoxide (DMSO; Sigma-Aldrich, USA) were added to 1000 mg/mL of dried plant extracts, and the terminal concentration was regulated to 500 mg/mL. Consecutive dilutions of plant extracts were prepared using sterile distilled water in the concentration range of 15.6-500 mg/mL. Then, an equal volume (100 μL) of the inoculum was evenly distributed on agar plates by sterile swap, and 5 wells were punched on SDA agar using a sterile borer after drying the plates for 5 minutes. The wells were poured with 100 μL of serial fold dilutions of plant extracts and the plates were incubated at 30°C for 24 to 48 hours.31 MICs were optically determined and defined as the lowest concentration of plant extract without optical growth. Moreover, minimum fungicidal concentrations (MFCs) were defined as the lowest concentrations of plant extracts without visible growth of more than four colonies, which corresponded to 99.9% of microbial mortality in primary inoculation.34

**Statistical Analysis**

The results of fungi growth inhibition zone diameters at different concentrations of the selected plants were adjusted for mean and standard deviation as well as confidence interval of 95%. Three-way analysis of variance (general linear model: GLM) was performed to investigate the differences among the selected plants, and the means of comparison were used to compare the differences of mean values between two plants by Student's t test separately.

**Results**

The anti-Candidial effectiveness of six herbs against C. albicans, C. glabrata, and C. tropicalis were assayed by AWDM. The zones of inhibition (ZOI) of the tested hydroethanolic extracts are shown in Table 2. The tested medicinal plants showed anti-Candidial properties in the range of 8-38 mm. The hydroethanolic extracts of ZMB, SAB, and CZL exhibited strong anti-Candidial properties, while the hydroethanolic extracts of PFL, TAPL, and TEPL revealed moderate activities at any of the tested concentrations. The highest inhibitory activities were the effect of CZL on C. albicans (ZOI: 38 mm) with MIC = 1.56 mg/mL (Figure 1) and that of Z. multiflora on

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**Table 1. Identification, Voucher Specimen, and Data on Traditional Use of the Studied Plants**

| Botanical Name     | Family    | Voucher  | Origin     | Local Name          | Plant Part | Traditional Use                                                                 |
|-------------------|-----------|----------|------------|---------------------|------------|----------------------------------------------------------------------------------|
| Zataria multiflora | Lamiaceae | Avishan  | N          | lv                  | leaves     | Antiseptic, anesthetic, antispasmodic                                              |
| Stachys acerosa    | Lamiaceae | Sonboleh | N          | lv                  | leaves     | Infection, asthma, Rheumatic, treat of skin, inflammatory disorders                |
| Prangos frulacea   | Asteraceae | Jashir   | N          | lv                  | leaves     | Feverfew, anti-migraine, anti-spas, Anti-pyretic,                                |
| Tanacetum parthenium | Asteraceae | Babueneh | E          | lv                  | leaves     | Anti-Migraine headaches, arthritis, reduce fever digestive problems               |
| Teucrium polium    | Lamiaceae | Kalpooreh| N          | lv                  | leaves     | Antidiabetic, anti-spasmodic, anti-inflammatory, analgesic, antioxidative, antimalarial |
| Cinnamon zeylanicum | Lauraceae | Darchin  | bk         |                     | bark       | antiseptic, analgesic, antispasmodic, antifungal, antioxidative, antibiotic, parasiticide, antidiabetic |

N: native to Iran; E: exotic; lv: leaves; bk: bark.

**Table 2. Anti-Candida Activity (Inhibition Zone, mm)* of Selected Medicinal Plant Extracts on Candida Species**

| Plant                  | 50 mg/mL | 25 mg/mL | 12.5 mg/mL | 6.25 mg/mL | 3.12 mg/mL | 1.56 mg/mL |
|------------------------|----------|----------|------------|------------|------------|------------|
| **C. albicans**        | C1  | C2  | C3  | C1  | C2  | C3  | C1  | C2  | C3  | C1  | C2  | C3  | C1  | C2  | C3  | C1  | C2  | C3  |
| Z. multiflora leaf     | 30 | 37 | 25 | 18 | 28 | 18 | 14 | 27 | 13 | 21 | 10 | 19 | 11 | 12 | 11 |
| C. zeylanicum stem     | 31 | 35 | 38 | 25 | 30 | 34 | 22 | 24 | 25 | 19 | 20 | 21 | 16 | 18 | 10 | 12 | 13 |
| S. acerosa leaf        | 26 | 30 | 20 | 23 | 23 | 17 | 16 | 18 | 15 | 15 | 15 | 11 | 13 | 11 | 11 | 11 | 11 |
| T. polium leaf         | 23 | 23 | 19 | 19 | 12 | 17 | 16 | 16 | 13 | 14 | 11 | 11 | 11 | 11 | 11 | 11 | 11 |
| T. parthenium leaf     | 17 | 23 | 18 | 15 | 18 | 11 | 13 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 |
| P. ferulacea leaf      | 18 | 23 | 11 | 13 | 19 | 16 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 |

*C1, Candida tropicalis; C2, Candida glabrata; C3, Candida albicans; NI: No inhibition.

Values represent the mean of three replicates.
C. albicans with MIC 6.25 mg/mL, C. glabrata (MIC 1.56 mg/mL), and C. tropicalis (MIC 12.5mg/mL). The lowest anti-Candidial property among the properties of these six plants was the effect of T. parthenium on C. albicans (ZOI: 8 mm) with minimum inhibitory concentration (MIC) = 50 mg/mL (Table 3). All the tests were performed in duplicate. Three-way analysis of variance (GLM) demonstrated a significant difference (P<0.05) for the effects of plant extracts at different concentrations on the selected fungi (Table 4). The comparison of differences in the mean values of non-growth halo diameters between two plants based on Student’s t test are shown in Table 5. According to these results, the means for non-growth halo diameters of the tested fungi by C. zeylanicum were higher than those for Z. multiflora extract, which were not significant (P=0.096); however, a significant difference was detected between the non-growth halo diameters of the fungi and other tested plants (P<0.05).

Discussion
Candida fungal agents are capable of causing superficial and deep fungal infections. Candida species have been identified as a major cause of hospital-acquired infections. Herbs are extensively used in traditional medicine because they are easily available and can be applied for curing a variety of ailments. In our study, the obtained MIC, and MFC, of the Z. multiflora extract were 6.25 mg/mL, 1.56 mg/mL, and 12.5 mg/mL for C. albicans, C. glabrata, and C. tropicalis, respectively, which was greater than the result on C. albicans gained for the essential oil of this extract in another study carried out by Zomorodian et al (MIC=0.062, MFC=0.125 μg/mL for C. albicans and C. glabrata, respectively, and MIC=0.25, MBC=1 μg/mL for C. tropicalis). The contradictory results may have been due to the differences of species of Z. multiflora, phytochemicals, or study methods. Also, another study reported anti-Candida activity of Z. multiflora Boiss with the MIC=70.7 mg/mL, which was more than the MIC found by our study. Previous studies had suggested that carvacrol and phenolic compounds in herbs may have played important roles in their antimicrobial effectiveness.

### Table 3. Anti-Candida Activity MICs (mg/mL) and MFCs of Selected Medicinal Plant Extracts on Candida Species

| Fungi       | Plants                              | Z. multiflora | C. zeylanicum | S. acerosa | T. polium | T. parthenium | P. ferulacea |
|-------------|-------------------------------------|---------------|---------------|------------|-----------|---------------|--------------|
| C. tropicalis| MFC                                 | 12.5          | 50.0          | 1.56       | 12.5      | 25.0          | 25.0         |
| C. glabrata | MFC                                 | 1.56          | 6.25          | 1.56       | 6.25      | 3.12          | 12.5         |
| C. albicans | MFC                                 | 25.0          | 6.25          | 1.56       | 3.12      | 12.50         | 50.0         |

Abbreviations: MIC, minimum inhibitory concentration; MFC, minimum fungicidal concentration.

Values represent the mean of three replicates.
disc diffusion method and the results had revealed a moderate antimicrobial activity against the examined microorganisms.8 These results were in agreement with the findings from our study, showing that Stachys acerosa had moderate anti-candida properties against C. albicans. In another study, antifungal properties of eight Cinnamomum (Lauraceae) species against dermatophytes (e.g., Trichophyton rubrum, T. mentagrophytes, T. tonsurans, Microsporum canis, M. gypseum, and M. audouinii) and one filamentous fungus (i.e., Aspergillus fumigatus), and different strains of yeasts (i.e., C. albicans, C. glabrata, C. tropicalis, C. parapsilosis, and Cryptococcus neoformans) had been explored. The results from this study had revealed that leaf and bark of C. zeylanicum had had the strongest properties against all the yeast with MIC values of 0.04 to 0.63 μg/μL, and the most resistant yeast had been that of C. glabrata, with MIC values > 1.25 μg/μL.59 These results were consistent with the findings from our study, which showed that C. zeylanicum had the most anti-candida properties against C. glabrata with MIC value 1.25 mg/mL. Another previous study had reported that C. albicans had been more sensitive to of T. parthenium (feverfew) compared to the Aspergillus niger and Candida cruise.60 These findings were not in agreement with those from our study which showed that feverfew had the most anti-Candida properties against Candida glabrata with MIC value 12.5 mg/mL. Masomi and Hassanshahian had investigated the antifungal activities of five herbs, namely Pistacia vera skin, Teucrium polium leaf, Trachyspermum ammi seed, Piper nigrum seed, and Camelia sinensis leaf extracts on C. albicans. All herbs had exhibited antifungal activities against C. albicans, but P. vera extract had shown the highest MIC and MFC values (6.25 and 12.5 mg/mL) on C. albicans with ZOI: 40 mm and Piper nigrum with ZOI: 13 mm had shown the lowest antifungal activity. However, T. polium extract had shown moderate antifungal activity with MIC and MFC values of 12.5 mg/mL and 50 mg/mL.61 This result was relatively consistent with the result from our study showing that T. polium had anti-candida properties against C. albicans with MIC and MBC values of 25 mg/mL and 50 mg/mL. Taking into account the results from our study as well as the limitations regarding the using of chemical antimicrobials due to their side effects and increased drug resistance, therefore, it was highly recommended that the chemical drugs be replaced with plants and natural elements.

### Conclusion

According to our study results, ZMB and CZL had considerable anti-Candidial properties compared to other plants examined in this study. Moreover, CZL showed stronger anti-Candidal activity compared to TAPL and TEPL. In sum, the ascending sequence of fungicidal growth inhibitor regions was as follows: C. zeylanicum > Z. multiflora > S. acerosa > T. polium > T. parthenium and P. ferulacea.

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### Authors’ Contribution
This study was regulated and supervised by NA. BS carried out microbiological examinations, statistical analyses, and manuscript preparation. ST, YY, and EA participated in collecting plants, preparing the extraction of medicinal plants, and performing microbiological experiments. SUN prepared and authenticated the selected medicinal plants.

### Conflict of Interests Disclosure
The authors have no conflict of interests to declare.

### Ethical Approval
This study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. The University Ethics Committee code number was IR. AJUMS. REC. 1397. 048.
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