

Evaluation of Antifungal Activity of Medicinal Plant Extracts on *Candida albicans*

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ABSTRACT

Today, opportunistic fungi, especially *Candida albicans*, are among the most common risk factors in patients with weakened immune systems. Fungal infections caused by *Candida* species and increasing number of azole-resistant strains are of great importance in immunocompromised patients. The toxicity of the drugs used, the development of resistance to these fungi, and the problems caused by drug interactions necessitate the use of more effective drugs with less toxicity. This study aimed to evaluate the antifungal activity of medicinal plant extracts on *C. albicans*. In this review study, Scopus, PubMed, MEDLINE, Google Scholar, SID, and Magiran databases were searched between 2000 and 2019 to identify related articles. The search keywords were “*Candida albicans*”, “Complementary”, “Herbal medicine” and their Persian equivalents. All in vivo and in vitro trials were included in the study. The reviewed studies showed the effectiveness of some compounds in inhibiting the growth of *C. albicans*. The results of the present research were in in-vitro conditions, but they need to be conducted in-vivo for human use.

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Introduction

Candida species are the most important causes of fungal infections in humans and animals. These fungal infections often occur in people with underlying factors such as cancer and leukemia, diabetes mellitus, long-term treatment with antibiotics and corticosteroids, AIDS, pregnancy, burns, and transplants. These infections vary from mucosal colonization to invasive and fatal infections. Among various clinical forms of infections, Cutaneous and mucosal candidiasis is more common (1).

Candida albicans is a two-dimensional fungus that causes diffuse and localized diseases in different people and is one of the most important causes of disabilities in patients with weakened immune systems (2).

Moreover, in healthy individuals, *C. albicans* causes diseases such as stomatitis due to dentures, the treatment of which is one of the most common treatments in the field of oral diseases. Although nystatin is used for treatment, different studies have shown resistance of different *Candida* species to antifungal drugs (3).

Drug resistance, toxicity, solubility, stability, and absorption are the most important problems. Furthermore, local infections are treated with nystatin, which has a very unpleasant taste. Therefore, the use of compounds with minimal side effects and having a desirable and acceptable taste in the treatment of lesions caused by *Candida* seems reasonable (4). *C. albicans* is normally a gastrointestinal microbiome, but when the host's immune system is compromised, it can

cause gastrointestinal candidiasis (5). *C. albicans* has the potential for coexistence and pathogenicity. This fungus can have yeast growth, true teliospore, biofilm, and false teliospore, and it is thus called polymorphic fungus which is an important pathogenic factor. Furthermore, the ability of fungi to bind and invade host body cells, secrete hydrolyzing enzymes, contact sensing and thigmotropism, and phenotypic switching are the features of *C. albicans* in pathogenic potential (6).

Flowers and plants are the most tangible creatures, and at the same time, the most eloquent manifestation of the power and greatness of creation.

According to the World Health Organization (WHO), more than 80 percent (nearly 5 billion people) still use herbal medicine to treat diseases (7).

Herbal medicines have many positive effects and they do not have any side effects. However, continuous and incorrect use of chemical drugs can cause fungal resistance and make drugs ineffective, and as a result, patients should take stronger chemical drugs (8).

Materials and Methods

In this review study, Scopus, PubMed, MEDLINE, Google Scholar, SID, and Magiran databases were searched between 2019 and 2000 to identify related articles. The search keywords were “*Candida albicans*”, “Complementary”, “Herbal medicine” and their Persian equivalents. All in vivo and in vitro trials were included in the study.

Results

Zingiber officinale

Ginger is a yellow plant with purple veins with the scientific name *Zingiber officinale*. Perennial ginger with a maximum height of 1.3 meters has a tuberous creeping rhizome and petioleless leaves in the size of 2 * 20 cm, bayonet or line that has a narrow tip and no hairs. Thick rhizomes of the plant form its medicinal part. Ginger is available in fresh (green), dried (brown), and cultivated forms. Commercial types of ginger are: Jamaican, Chinese, and African. Australian and Indian gingers are the best varieties used for medicinal purposes. Jamaican ginger is marketed in a completely shaved and cleaned form. Its uses include the treatment of motor disabilities and indigestion. It is also used as a flavoring and appetizing spice in the food industry, and the side effects include dermatitis in very sensitive people (9). Its main constituents include a variety of sugars (1-3%), fats (1-3%), spicy crabs (0.2%), and oleoresin (2-3%). These spicy ingredients that make up the smell and taste of ginger root include ginger, zingerone, shingles, gingerol, and zebrafish (10).

Allium cepa

Allium is an underground fleshy tuberous plant of the tulip family with the scientific name of *Allium cepa*.

Onions have an aerial part and an edible root part. The smell and taste of onion is related to the composition of the environment and its genetics. The smell of onions is related to volatile sulfur substances that decompose during distillation at normal room temperature.

Allium flavonoids are chemical compounds that are active against microorganisms and have an antibacterial effect against the growth of microorganisms in the laboratory (11).

Momeni *et al.* investigated the effect of onion extract on *C. albicans* and reported that *C. albicans* was semi-sensitive, sensitive, and resistant to crude extract, cold water extract, hot water extract, and alcoholic extract (12).

In a study by Tabatabaei Yazdi *et al.*, who examined the effect of ginger, the results indicated that the highest and lowest diameters of inhibition zone halo were observed at a concentration of 100 mg/mL on *Candida albicans* and *Salmonella Typhi* (*S. Typhi*). The minimum inhibitory concentrations of ginger essential oil were equal to 50, 50, 25, 6.25, 12.5, 12.5, 6.25, and 6.25 mg/mL for *Pseudomonas aeruginosa*, *S. Typhi*, *Escherichia coli*, *Staphylococcus aureus*, *Listeria innocua*, *Bacillus cereus*, *C. albicans*, and *Aspergillus niger* (13).

Bunium persicum

Bunium persicum is a small, herbaceous, and perennial plant of the umbrella family that is native to a limited area of West Asia. The Iranian type of this plant grows in hot and dry areas such as Kerman, and also in the heights of some cold regions such as Urmia and Alborz heights (14).

This plant has some therapeutic effects on gastrointestinal and bladder disorders and is known as an antihistamine, anticonvulsant drug, repellent of intestinal worms, anti-asthma, and anti-respiratory disorders in traditional medicine (15).

In a study by Rashidi *et al.*, who examined the antifungal activity of *Carum carvi* essential oil, the results indicated that *Candida albicans* yeasts grew in all plates of the control group after the first 24 hours, but no growth groups were observed in none of the 1 mg/mL of essential oil. All plates of the control group and plates containing 3 mg/mL of essential oil and 2 mg/mL of *Carum carvi* grew at the second 24 hours (16).

Teucrium

Teucrium is a perennial herbaceous branched plant with a height of 3 to 35 cm, narrow. This plant has white and yellowish flowers. The medicinal organ of *Teucrium* is the flowering branch head that flowers in summer from June to August. The extract of this plant contains Diterpenoids, 5, 7 glycosides, 6 methoxy gengenane, thymol, carvacrol, and volatile essential oil, and most of the essential oil includes β -caryophyllene/germacrene D, Humulene, and Caryophyllene oxide (17).

In a study by Shoaei *et al.*, the minimum inhibitory concentration of *Teucrium* extracts on *C. albicans* was 1000 µg/mL, indicating a significant difference ($P=0.002$) (18).

Ficus

Ficus is one of the oldest and most widely consumed fruits in the world and it has been known to humans since ancient times (19). This fruit grows from the fig tree with the scientific name of ficus (20).

It has been cultivated for 11,000 years and was one of the first plants to be cultivated (21) as this fruit was given as food to Olympic champions during their training and it was even given to the winners of the first Olympic competitions as medals (22).

From ancient times, different parts of this plant, including sap, fruit, and leaves have been used for medicinal purposes (23). Since climatic conditions affect the quality of this fruit, the best dry figs grow in few areas of winding valleys where temperature, relative humidity, and wind flow are suitable for their production. However, the production of fresh figs seems to require less specific climatic conditions (24).

The geographical distribution of figs in southwestern Asia and the eastern Mediterranean (21) extends from Turkey in the east to Spain and Portugal in the west. It also grows in some regions of the United States, Chile, Saudi Arabia, Iran, India, and Japan (21).

According to Traditional Iranian Medicine (TIM), the fig is the fruit of a tree with the same name that has Barri, Bostani, and mountain varieties. It is a medium-sized tree with broad leaves. The best figs are juicy and sweet, and the white type has more nutritional properties, while the black type has better medicinal effects (23). This fruit is sweet, contains a large number of kernels, and is often eaten dry. Figs have been mentioned in the ancient Jewish and Greek scriptures (25).

This fruit is laxative and is effective in treating various diseases including hemorrhoids, gout, leprosy, and epilepsy (26). Other benefits of figs include lowering blood pressure, lowering blood cholesterol and triglyceride levels, preventing cancer and inflammation, anti-intestinal worms (28), anti-asthma (27), anti-cough, treating skin diseases (27), gonorrhea, warts, reduction of menstrual pain (26), diarrhea (25), improving constipation (25), boosting the immune system, antimicrobial, antiviral effects (26), improving liver diseases (25), preventing muscle cramps, reducing fever and weight, emollient properties, boosting sexual potency, reducing chest pain, and expectorant effect (20).

Berberis vulgaris L

Barberry shrub with the scientific name of *Berberis vulgaris L* with irrigation cycle is about twice as long as normal plants and it has withstood years of drought well. The source of income for many rural families in South Khorasan is dependent on barberry. This shows

the special importance of this product in the agricultural and economic situation of the region (29).

Other medicinal properties of this plant include the treatment of liver diseases, antioxidant, anti-parasitic, anti-inflammatory, and reducing blood sugar, cholesterol, triglyceride, and high blood pressure. This shrub has more than 200 years of age in South Khorasan province and is a major agricultural crop, especially in Qaen and Birjand counties.

As reported by Heidari *et al.* (30), these two cities with a cultivation area of nearly eight thousand hectares allocate for more than 31% of Iran's *Berberis* cultivation area and 35% of the world's *Berberis* production. According to available statistics and data, the average annual production of *Berberis* is about 3.2 thousand tons with an average yield of 1200 kg in South Khorasan province (31).

On the other hand, barberry is the only product of farmers in some areas and the income of many households depends on the cultivation of this product (32).

Ginseng

Ginseng root is a Chinese medicine that has long been used to stimulate appetite, relieve depression, boost the immune system, relieve pain, and improve mental and physical functions. The roots of this plant contain Triterpenoid saponins, essential oils, polyacetylene, polysaccharides, peptidoglycans, nitrogenous compounds, fatty acids, carbohydrates, and phenolic compounds (33).

In a study by Tajik Ijdan, the lowest and highest levels of MIC (Minimum Inhibitory Concentration) were respectively 0.0625 and 0.5 µg/mL in *C. albicans* and *Candida krusei* for itraconazole by a microdilution method, while the lowest MIC and MFC (Minimum Fungicidal Concentration) were 64 mg/mL for the alcoholic extract. The maximum halo diameter for *C. albicans* strain was 14 mm for alcoholic extract, and the halo diameter range was 14-32 mm for itraconazole. There was no significant difference between alcoholic extracts with dilutions of 64 and 128 mg/mL with the drug in the two methods. ($P<0.05$) (34).

Lavandula angustifolia

Lavender, scientifically named *Lavandula angustifolia*, is a perennial and evergreen plant of the mint family. Its height is between 30 and 60 cm and the flowers are terminal clusters and complex at the top of the stem.

The plant contains essential oils and monoterpenes, the most important constituents of which are linalyl acetate, linalool, beta-osmin, cineole, camphor, and sesquiterpene. In the past, aerial parts and lavender flowers were used for various medicinal purposes.

It is effective in treating stomach diseases, headaches, and especially stress headaches. In

addition, it has analgesic, antispasmodic, antimicrobial, sedative, and antibacterial properties.

Querques infectoria

Mazo with the scientific name of *Querques infectoria* is one of the most important medicinal plants in the Zagros Mountains. It has been known and used as a medicinal plant since ancient times.

Mazu tree has been shown to have a wide range of medicinal properties such as antiseptic, antioxidant, anti-diabetic, anti-tremor, antibacterial, antifungal, anti-viral, and anti-inflammatory effects (35).

Querques infectoria mazo is a rich source of tannins and it has small amounts of gallic acid and alginic acid which have a positive effect against tooth decay (36). This plant has been shown to be a rich source of antibacterial agents (37).

Glycyrrhiza glabra

Glycyra is a perennial herbaceous plant belonging to the genus Butterfly (38). It is native to the Mediterranean, southern Russia and Asia, but is now cultivated throughout Europe, the Middle East, and Asia (39).

There are 30 species of glycyrrhiza in the world and 3 species in Iran; and the most important species is *Glabra*. This species grows in all regions of the north, south, east, and west, including West Azerbaijan, around Tabriz, Golestan, Khorasan, Kerman, and Jajrud. In addition, *Achinata* and *Spesimal* species are grown in Iran (40).

This plant is one of the most important medicinal and industrial plants whose active ingredients are used in various forms. The compounds obtained from it are used in the pharmaceutical, food, and health industries (41).

Iran is one of the countries exporting licorice root, so that the export of its extract during the years 2002 to the first eight months of 2009, was 35.4 thousand tons (economic value of \$ 92.3 million). Currently, most exports of licorice root in Iran are from Fars province to Germany (42).

This plant is self-growing in different parts of Iran. Since this plant is uprooted from the ground, its amount is gradually reduced in nature; therefore, in the southern provinces of Iran (especially Fars and Kerman provinces) this plant is in danger of extinction (43).

Licorice is used in the food industry as a flavoring for canned goods, confectionery, chocolate, candy, soft drinks, sausages, and also for sweetening cocoa. According to the monograph of the German Drug Commission, Licorice has therapeutic properties and is ranked as one of the treatments in the World Health Monograph (39).

Honey

For thousands of years, humans have used a mixture of bee saliva and flower nectar called honey as a

medicine to treat diseases. Honey contains compounds of organic acids, amino acids, minerals, polyphenols, vitamins, and aromatic compounds.

In addition, the antimicrobial and antioxidant activity of honey is due to the activity of enzymes such as glucose oxidase and catalase, as well as phytochemical compounds such as ascorbic acid, flavonoids, phenolic acid, carotenoid derivatives, amino acids, proteins (44).

Studies have shown that honey has antimicrobial properties. In addition, it has an inhibitory effect against *C. albicans* (45).

In a study by Banaeian-Borujeni *et al.*, the anticandidal effect of honey and miconazole against *C. albicans* was shown. In vitro, it was shown that honey at a concentration of 08% significantly inhibited the growth of *C. albicans*.

Miconazole, on the other hand, completely inhibited the growth of *C. albicans* (45).

Crocus stivus L

Dried saffron is the stigma of *Crocus stivus L*. The plant is officially listed as a Chinese medicine and has been used in traditional Chinese medicine as a sedative to treat hematoma, monostasis, depression, and seizures (46).

Recent studies have shown that this plant has the potential to reduce the risk of various diseases (47). Several medicinal properties have been mentioned for saffron. Some metabolites derived from saffron stigma have shown many therapeutic effects due to their hypolipidemic, antitussive, antioxidant, anti-diabetic, and other functions. Aqueous and alcoholic extracts of saffron protect the heart and fight neurodegenerative disorders.

Numerous medicinal properties of saffron are related to its various components, such as Crocetin, Crocin, and other substances that have strong antioxidant properties and accumulation of oxygen free radicals and pro-inflammatory cytokines (48).

Studies have shown that there are more than 150 different substances in saffron stigmas. The strongest components of saffron are carotenoids and monoterpene aldehydes. The study of the relationship between the function and structure of the molecule has shown that some properties of saffron are due to its deglycosylated derivatives, and others are related to glycosylated derivatives (49).

Discussion

The most important cause of nosocomial fungal infections is *Candida* yeast. This fungus can cause many clinical symptoms such as thrush, vaginitis, skin infection, endocarditis, meningitis, brain abscess, in human host, in favorable conditions. The resistance of microorganisms to antimicrobial agents is increasing; therefore, recognizing new antimicrobial compounds

with less side effects is of great importance. Limitations such as the low number of antifungal drugs, their toxicity to the body's cells, or the reduced sensitivity of some *Candida* species to these drugs have always been a major problem in treatment. Therefore, the use of plant compounds is useful for killing microorganisms.

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Conflict of Interest

The author declared no conflict of interest.

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