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# Exploring antifungal activities of *Tamarix aphylla* and *Zygophyllum album* extracts against human mucormycosis

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## Abstract

Recent studies concerned with various medicinal plant ingredients which have antimicrobial activities have directed special attention toward the pathogenic microorganisms such as bacteria and fungi. Fungal diseases severity increases in immunosuppressed persons, which impacts the public health. The purpose of this research was to study in vitro antifungal effects of some nontraditional medicinal plants in Saudi Arabia (*Tamarix aphylla, Zygophyllum album* and *Suaeda palaestina*) against some pathogenic fungi through extraction of the active ingredients of each plant (phenolics, flavonoids, etc.). The present research was conducted to evaluate antifungal activity of *T. aphylla* and *Z. album* leaf extracts against Mucormycosis "black fungus" pathogenic fungi. Leaves of *Tamarix aphylla* and *Zygophyllum album* were obtained, rinsed, dried, ground, and extracted using methanol (70%) and distilled water solvents. GC-MS analysis of the essential oil of plant extracts was carried out for antifungal activity assays. he results were aqueous extraction at 500 ppm mean measured at about 10±0.40 mm, while aqueous extraction at 1000 ppm measured about 14 ±0.70 mm; on the other hand, methanollic extraction at 500 ppm was about 16 ±0.80 mm, and methanollic extraction at 1000 ppm detected about 23 ±0.99 mm of of *Tamarix aphylla* extraction. The inhibitory effect of *Zygophyllum album* in aqueous extraction at 500 ppm mean measured about 8±0.22 mm, while aqueous extraction at 1000 ppm measured about 18 ±0.60 mm; on the other hand methanollic extraction at 500 ppm was about 10±0.41 mm, and methanollic extraction at 1000 ppm detected about 20±0.56 mm. Obtained results indicated that *Tamarix aphylla* and *Zygophyllum album* had nearly similar inhibitory effects, with slightly more patent effect of methanollic extraction at 1000 ppm *Zygophyllum album*.

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**Introduction**

COVID-19 has recently been linked to many significant issues, some of which are thought to be more hazardous than the coronavirus infection itself. Even though the majority of these infectious agents were quite insignificant in healthy individuals, they became deadly in combination with a coronavirus infection. *Mucormycosis* "black fungus," also known as zygomycosis, is related to *mucormycetes* mold types including *Mucor*, *Lichtheimia*, *Syncephalastrum*, *Rhizomucor*, *Apophysomyces*, *Rhizopus* and *Cunninghamella bertholletiae* species, which spread throughout the environment (decaying matter, soil, rotten wood, compost piles and leaves) and are considered one of the more dangerous rare fungal infections. The prevalence of this fungus has significantly increased among immunocompromised patients and those who take medications that impair immunity or reduce the body's natural defenses against pathogens (Martinelli *et al.*, 2021).

Infections such as *mucormycosis* can spread to the skin through burns, wounds, scrapes, and any type of skin incision, as well as after one inhales fungal spores from the environment. The spores that are inhaled mostly damage the sinuses and lungs after passing through the upper respiratory system. Depending on where in the body the fungus is developing, *mucormycosis* symptoms vary. Symptoms of rhinocerebral (sinus and brain) *mucormycosis* include headache, sinus or nasal congestion, immediately worsening black lesions on the nasal bridge or upper interior of the mouth, and fever. Fever, cough, chest pain, and shortness of breath are among the signs and symptoms of pulmonary (lung) *mucormycosis*. Blisters or ulcers may appear as a result of cutaneous (skin) *mucormycosis*, and the affected region may turn black. Pain, warmth, extreme redness, or swelling near a cut are further signs. The symptoms of gastrointestinal *mucormycosis*, on the other hand, include abdominal pain, nausea, and vomiting as well as bleeding in the intestines. It might be challenging to determine which symptoms are caused by *mucormycosis* because diffused *mucormycosis* generally affects persons who are already suffering from other illnesses. Patients who have a disseminated infection in the brain may experience changes in mental state or coma (Sharma and Goel, 2022).

The salt cedars (*Tamarix* spp.), which are invasive, exotic, deciduous, small trees and shrubs, are members of the Tamaricaceae family. The largest species of Tamarix, *Tamarix aphylla (L.),* which may reach heights of up to 18 meters, is found in Central Asia, North Africa, and Southeastern Europe (Abdallah and El-Ghazali, 2013; Sadafbibi *et al.*, 2015). *T. aphylla* leaf extracts are utilized as an anti-inflammatory and antioxidant ingredient in the healing of wounds (Zain *et al.*, 2012; Iqbal *et al.*, 2013). The *T. aphylla* extract's phytochemical analysis revealed the presence of components such as glycosides, alkaloids, phenolics, tannins, and saponins (Emad and Gamal, 2013). *Zygophyllum album* L. (*Tetraena alba*) is a member of the Zygophyllaceae family, which is found in steppe and desert ecosystems from the Mediterranean to central Asia, South Africa, and Australia. The *Zygophyllum* genus is widely used in traditional medicine around the world for a variety of ailments, including the treatment of diabetes, wound care, dental caries treatment, and hair and face care, in addition to its anti-inflammatory, antifungal, antibacterial, and anticancer properties (Ebrahim *et al.*, 2018; Shawky *et al.*, 2019). The phytochemical components of *Z. album* include essential oils, phenolic compounds, triterpenes, flavonoids, and sterols (El-Shora *et al.*, 2016; Soumaya *et al.*, 2017).

Among the many methods for preventing fungal infections, chemical control is still one of the most important because it can reduce the incidence of fungal infections without the worry of secondary side effects or the development of microbial resistance to the chemicals. In order to safeguard coronavirus patients, researchers are looking for naturally occurring antifungal medicines that may be employed. The goal of the current study was to determine the antifungal efficacy of *Z. album* and *T. aphylla* leaf

extracts against pathogenic fungi that cause the "black fungus" disease *Mucormycosis*.

## Material and methods

*Plant collection*

Leaves of *Tamarix aphylla* and *Zygophyllum album*, about 1 kilogram from each plant, were collected during January 2021 from saline soil of the Taiba region (latitude: 21.7874726, longitude: 39.1459682), about 17 kilometers from the Red Sea. The collected plants were labeled and transported to the laboratories of the College of Science, University of Jeddah, where the obtained leaves were rinsed, dried, ground by blender, sieved using a 1mm aluminum sieve, and stored inside labeled airtight bottles until used (Seo *et al.*, 2014).

*Plant extraction*

*Extraction techniques*

Extraction techniques utilized four solvents: methanol (70%) and distilled water. Briefly for each solvent, 100g dry powder was extracted with 1000ml and 500ml solvents by maceration at room temperature for 48 hours. Then two filtrations of each mixture were run through N°1 Whatman paper and filter paper (0.45µm porosity). The collected filtrates were dried separately at 50°C using a Laborota 4000 rotary evaporator. Aqueous and aqueous methanol crude extract powder were used for investigate phytochemical compounds, determination of total phenol content and antioxidant screening (El-Shora *et al.*, 2014).

*Test fungal organisms*

The Test Fungal Organisms in the present study *Mucormycosis* "black fungus" were collected from Department of Microbiology, College of Science, University of Jeddah.

*Antifungal activity examination*

For antifungal activity assays, a stock solution was made for each extract with 0.2 g/mL in dimethyl sulfoxide (DMSO). The extracts were stored at 20°C until further use and the stock were stored at 4°C until used. The fungicidal activity of extracts was assessed by the agar well diffusion method using Sabouraud's Dextrose Agar, incubated at 28±2˚C/7d, and examined regularly for fungal growth to determine the minimum inhibitory concentration (MIC) in millimeters (mm). The antifungal activity was repeated twice with two replicates for all clinical isolates with each plant extract at all the test concentrations (Indu *et al.*, 2006). The test extracts of desired concentrations (500 ppm, 1000 ppm) in Aqueous and methanollic solvents were each inoculated with an inoculum of 5mm diameter for each extract and incubated for seven days (Zohra *et al.*, 2013).

*Electron microscope*

Samples were fixed by gluteraldhyed 2.5% and dehydrated by ethanol with agitation using an automatic tissue processor (Leica EM TP, Leica micrososystems: Austria). Then the samples were dried using CO in a critical point drier (Model: Audosamdri-815, Tousimis; Rockville, Maryland, USA). The sample was coated by a gold sputter coater (SPI-Module, USA). The samples were observed by scanning electron microscopy (model: JSM-5500LV; JEOL Ltd –Japan).

*Statistical analysis*

The data were expressed as means ± standard error (SE) and analyzed using SPSS 11.0 for Windows. One-way analysis of variance (ANOVA) and multiple comparisons were carried out to test any significant differences between the means. Differences between the means at the 5% confidence level were considered significant. Correlations between variables were computed using the regression model in SPSS 11.0 for Windows.

## Results

*Antifungal activity of Tamarix aphylla and Zygophyllum album extracts against Mucormycosis "black fungus"*

Fig. 1 and Table 1 show the inhibitory effect of *Tamarix aphylla* in (I) were: (A1) Aqueous extraction at 500 ppm mean measured about 10±0.40 mm, while (A2) Aqueous extraction at 1000 ppm measured about 14±0.70 mm; on the other hand, (B1)

methanollic extraction at 500 ppm was about 16 ±0.80 mm and (B2) methanollic extraction at 1000 ppm detected about 23±0.99 mm. The inhibitory effects of *Zygophyllum album* in (I) were: (A1) Aqueous extraction at 500 ppm mean measured about 8±0.22 mm, while (A2) Aqueous extraction at 1000 ppm measured about 18±0.60 mm; (B1) methanollic extraction at 500 ppm was about 10±0.41 mm and (B2) methanollic extraction at 1000 ppm detected about 20 ±0.56 mm.

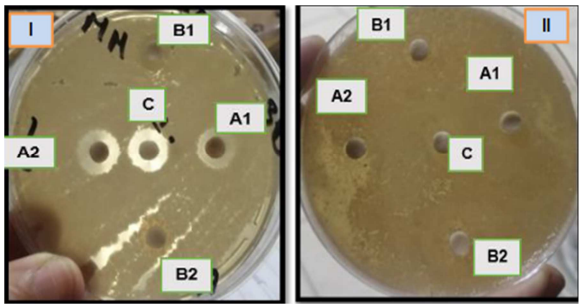


**Fig. 1.** Antifungal activity of *Tamarix aphylla* and *Zygophyllum album* extracts against Mucormycosis "black fungus": (I) represents *Tamarix aphylla,* while (II) represents *Zygophyllum album;* (A1) Aqueous extraction at 500 ppm, (A2) Aqueous extraction at 1000 ppm, (B1) methanollic extraction at 500 ppm, (B2) methanollic extraction at 1000 ppm

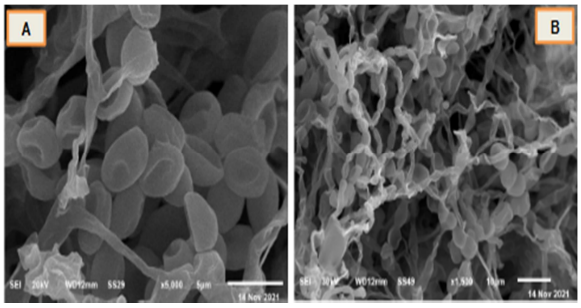


**Fig. 2.** Scanning Electron Microscope of Antifungal activity of *Tamarix aphylla* and *Zygophyllum album* extracts against Mucormycosis "black fungus": (A) represents the fungal cell at ×5000, (B) represents the fungal cell at ×1000

*The effects of Tamarix aphylla and Zygophyllum album extracts on the morphology of normal Mucormycosis "black fungus"*

Fig. 2 shows the changes which occur by addition of different concentrations of *Tamarix aphylla* and *Zygophyllum album* extracts compared with the normal shape of *Mucormycosis* "black fungus" by the Scanning Electron Microscope (SEM) pictures at two different focal lengths: X5000 and X1000. Fig. A shows that the *Mucormycosis* "black fungus" appeared as ovoid "yeast" cells with budding. Although figure (B) shows the shape changes of the fungus cells and their colonies, this change started as shrinkage that appeared in the usual oval shape; also, the previous stacking of cells in the colony was lost when exposing *Mucormycosis* "black fungus" to *Tamarix aphylla* and *Zygophyllum album* extracts. Exposure to higher concentrations of the plant extracts led to deformation until the shape of cells completely disappeared and the colony cells were interfered with due to the severity of the deformation.

**Table 1.** Antifungal Assay of *Tamarix aphylla* and *Zygophyllum album* extracts against *Mucormycosis* "black fungus"

| Solvent | Conc. | *Tamarix aphylla* | | *Zygophyllum album* | |
|---|---|---|---|---|---|
| | | 500 ppm | 1000 ppm | 500 ppm | 1000 ppm |
| Aqueous | Minimum | 00 | 00 | 00 | 00 |
| | Maximum | 25 | 40 | 10 | 23 |
| | Mean | 10±0.40 | 14±0.70 | 8±0.22 | 18±0.60 |
| Methanol | Minimum | 9 | 13 | 00 | 00 |
| | Maximum | 28 | 34 | 15 | 25 |
| | Mean | 16±0.80 | 23±0.99 | 10±0.41 | 20±0.56 |

## Discussion

An exponential growth rate of *mucormycosis* linked with COVID-19 has been observed. The capacity of the fungal spores to germinate in the favorable conditions created by COVID-19 patients' respiratory systems is the primary cause of the spread of this opportunistic fungal infection (Mahalaxmi *et al.*, 2021), which emerges once the patient's natural immunity is destroyed by the extremely contagious virus (Chauhan *et al.*, 2021). Numerous incidences of *mucormycosis* were documented in India in individuals recovering from COVID-19 who had a history of diabetes or other comorbidities. After an initial recovery, 37% of people with *mucormycosis* were found to have a history of COVID-19 (Hussain *et al.*, 2021). The fatality rate for *mucormycosis* was 50% before the COVID-19 epidemic. However, it has

increased to 85% during the current pandemic in India (Aranjani *et al.*, 2021).

Patients' development of a secondary opportunistic infection like *mucormycosis*, also known as a black fungus, during COVID-19 has been significantly influenced by their intermittent use of steroids, supportive oxygen from cylinders, and ventilators (in critically ill patients). *Mucormycosis* is a serious fungus infection that is angioinvasive and spreads quickly to other parts of the body. *Mucormycosis* can have devastating effects and be fatal to the persons who have it if it is not identified and treated quickly. In these situations, the patient needs immediate surgical intervention to stop other vital organs from becoming infected. Since mucormycosis is an opportunistic illness, it is frequently misdiagnosed and has a poor prognosis (Van *et al.*, 1999). Mucormycosis-causing pathogens are frequently diagnosed in low- and middle-income nations, including India, based on phenotypic traits such growth rate, colony morphology, and reproductive structures (Skiada *et al.*, 2018).

*T. aphylla* is a wild edible plant that is inexpensive and considerably improves human health in terms of disease treatment and prevention. *Tamarix aphylla* might be an excellent choice due to their strong efficacy in controlling plant diseases, which could lessen the risk to human health posed by some synthetic fungicides (Prakash *et al.*, 2019; Dilek *et al.*, 2021). The results of the current investigation showed that plants are a significant source of chemicals that may be helpful in the creation of novel antifungal medications. All of the examined plant extracts that were evaluated in various solvents showed varying levels of antifungal activity in a dose-dependent manner.

*Antifungal activity of Tamarix aphylla and Zygophyllum album extracts against Mucormycosis "black fungus"*

The inhibitory effect of *Tamarix aphylla* in (I) was (A1) Aqueous extraction at 500 ppm mean measured about 10±0.40 mm., while (A2) Aqueous extraction at 1000 ppm measured about 14±0.70 mm; on the other hand (B1) methanollic extraction at 500 ppm was about 16 ±0.80 mm and (B2) methanollic extraction at 1000 ppm detected about 23±0.99 mm. The inhibitory effect of *Zygophyllum album* in (I) was (A1) aqueous extraction at 500 ppm mean measured about 8±0.22 mm, while (A2) aqueous extraction at 1000 ppm measured about 18±0.60 mm; (B1) methanollic extraction at 500 ppm was about 10±0.41 mm and (B2) methanollic extraction at (1000 ppm) detected about 20 ±0.56 mm.

Similar results were reported by Pal *et al.* (2021), who assayed the antifungal properties of *T. aphylla* methanolic extract, which had antifungal activity (97.68%±0.58) against growth of *mucor spp.* and *F. oxysporum,* followed by ethanolic extract (97.37%±0.33) against *A. niger*. Palermo *et al.* (2020) regarded the antifungal potential of the ethanol extract of *T. aphylla* stems and leaves. Reid *et al.* (2020) mentioned that the crude ethanolic extract of *T. aphylla* leaves exhibited significant antifungal activity. The leaves' methanolic extracts from *T. aphylla* were recognized for their antiaflatoxigenic and antifungal actions. Similarly, the results of this study regarding the ethanol extract are in agreement with the findings of other authors (Skiada *et al.*, 2020; Eucker *et al.*, 2001; Ali *et al.*, 2019; Chander *et al.*, 2018; Alshehri *et al.*, 2021).

*The effects of Tamarix aphylla and Zygophyllum album extracts on the morphology of normal Mucormycosis "black fungus"*

Fig. 2 showed the changes which occurred through the addition of different concentrations of *Tamarix aphylla* and *Zygophyllum album* extracts compared with the normal shape of *Mucormycosis* "black fungus" using the Scanning Electron Microscope (SEM) pictures at two different focuses: X5000 and X1000. Fig. (A) showed that the *Mucormycosis* "black fungus" appeared as ovoid "yeast" cells with budding; figure (B) showed the shape changes of the fungus cells and their colonies. This change started by as shrinkage that appeared in the usual oval shape; also, the previous stacking of cells in the colony was lost

when exposing *Mucormycosis* "black fungus" to *Tamarix aphylla* and *Zygophyllum album* extracts. Exposure to higher concentrations of the plant extracts led to deformation until the shape of cells completely disappeared and the colony cells were interfered with due to the severity of the deformation. These findings agreed with previous studies showing that the active components found in *T. aphylla* extract disrupted and altered fungal growth (Sarkar *et al.*, 2021; Singh *et al.*, 2021; Fatimah *et al.*, 2023).

Obtained results proved that *Tamarix aphylla* and *Zygophyllum album* had nearly similar inhibitory effects, with slightly more potency of methanollic extraction at 1000 ppm for *Zygophyllum album*.

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