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Effect of different chest disorders on the severity and spreading of human mycotic pulmonary infections

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Abstract
A survey was carried out on patients clinically diagnosed with pulmonary diseases of different types through regular visits to the intensive care unit (ICU), Chest Hospital, Tanta University. The present study recorded Penicillium sp. as the most common fungus among patients with asthma, cough, DM and antibiotic abuse. *Heliotropium europaeum* was a wild plant was collected from Halayeb and Shalateen reserved region. It was tested as antifungal natural product, giving high activity with low MIC value at 25 mg/ml against the most dominant fungus, in comparison with a commercial standard.

Keywords: Penicillium, mycotic pulmonary infection, chest diseases, *Heliotropium europaeum*, antifungal treatment.

Introduction

Chest mycotic infections, or pulmonary fungal infections, involve various fungal pathogens that target the respiratory system, particularly the lungs. These infections are increasingly common, especially among immunocompromised patients, and can present significant diagnostic and therapeutic challenges. Due to the overlap of symptoms with bacterial and viral respiratory infections, fungal infections are often misdiagnosed or overlooked, potentially leading to delayed treatment and worsening outcomes (Debnath *et al.*, 2022) [3].

Certain factors can significantly increase an individual's susceptibility to fungal infections in the respiratory system. These factors either weaken the immune system, alter lung structure, or increase exposure to fungal spores, making it easier for fungal pathogens to establish infection. The primary predisposing factors include Immunosuppression is one of the most critical risk factors for chest fungal infections, as a weakened immune system is less capable of detecting and eliminating pathogens. The immune system plays a crucial role in preventing fungal spores from establishing an infection, but when it is compromised, the body is less able to fight off these pathogens (Chu *et al*., 2021) [2].

Asthmatic patients, especially those on long-term corticosteroid therapy, are at increased risk of allergic fungal infections, such as Allergic Bronchopulmonary Aspergillosis (ABPA). ABPA occurs when fungi like *Aspergillus fumigatus* trigger an exaggerated immune response in the airways, leading to inflammation, mucus production, and lung damage. Bronchiectasis: This condition involves the permanent dilation of the bronchi due to repeated infections or inflammation. Dilated airways in bronchiectasis patients often trap mucus and create pockets where fungi can colonize and grow, increasing the risk of fungal infections (Oliveira *et al*., 2023) [13].

Chest fungal infections represent a significant health challenge, especially in immune-compromised populations. Although advances have been made in diagnostic methods and treatments, several hurdles remain, including the toxicity of available antifungal agents, the development of resistant fungal strains, and the difficulty of early detection. Continued research is essential to improving diagnostic accuracy, developing safer and more effective antifungal treatments, and addressing the growing burden of fungal infections, particularly in regions like Egypt where environmental conditions and healthcare limitations exacerbate the problem. The development of new treatments, especially those targeting resistant strains and minimizing side effects, will be crucial in managing this rising global health issue (Kelly *et al*., 2020) [7].

Materials and methods

A survey was carried out on patients clinically diagnosed with pulmonary diseases of different types. That was achieved by arranging regular twice-weekly visits to the intensive care unit (ICU), Chest Hospital, Tanta University. Then patients clinically suspected to have mycotic pulmonary infection were assigned for more detailed lab studies.

Samples were taken from patients diagnosed clinically to have a mycotic pulmonary infection by sterile suction for mechanical ventilation (Margo and Brinser, 1987) [11]. The protocol of sampling and patient dealing was approved by the Research Ethics Committee, Faculty of Medicine, Tanta University, with an approval code of 36264MS320/9/23.

Each sample was cultured on three sterilized Petri dishes, containing sterile Sabouraud's dextrose agar (SDA) medium. All plates were incubated at 27°C for 14 days. Fungal colonies were purified for identification on the same nutrition medium. All purified fungal plates were examined to be identified. The following references were used for the identification of different fungal genera, and species: Moubasher (1993) [12], Klich (2002) [8], and Samson *et al*. (2010) [15].

A wild plant was collected from Halayeb and Shalateen reserved region during a field trip. The procedure described by Kasim *et al.* (2016) [6] with some modifications was followed to prepare the ethanolic extract of the dried plant. A weight of 1 g of the dried plant powder was well mixed with 5 ml of ethanol. Then incubated in the dark for 24 h. on an orbital shaker set at 120 rpm. After that, the extract was once filtered using non-absorbent cotton and twice using Whatman No. 1 filter paper, air-evaporated till dryness,

redissolved in 1000 ml distilled water and then kept at 4 °C for further work.

Half-fold serial dilutions were made for both the plant extract and commercial antifungal agent individually to prepare concentrations of 12.5, 25, 50, 100 and 200 mg/ml in distilled water, zero concentration was considered a negative control. A previously prepared pure spore suspension of the selected fungus (1 ml of about 10^6 cells/ml) was mixed with 1 ml of each concentration in sterile test tubes, completed with 8 ml of Sabouraud's dextrose broth medium and incubated at 27°C for 3 days, then optical density of growth was measured by spectrophotometer (Riele 5010, Germany) at 620 nm for each incubated mixture, results were tabulated and represented graphically, and MIC was recorded for each tested agent (Shadomy *et al*., 1985) [16].

Results

Fungal chest infection was surveyed by regular visits to Tanta University Chest Hospital. Incidence of mycotic infection was associated with different chest diseases, whereas the highest incidence rate associated with patients suffering from Asthma and Chronic Obstructive Pulmonary disease (20 cases= 33.33% for each), followed by bronchiectasis (10 cases = 16.67%), pneumonia (5 cases = 8.33%), tuberculosis (4 cases = 6.67%) while the lowest rate was recorded with ILD (1 case = 1.67%), as shown in Table (1).

These records were confirmed by distribution of symptoms in Table (2), the highest rate of infection recorded by patients has cough and dyspnea (60 cases = 100% for each), followed by expectoration (50 cases = 83.3 %), wheeze (30 cases = 50%), constitutional symptoms (40 cases = 66.6 %), while the lowest rate recorded by hemoptysis (10 cases = 16.6).

The severity of mycotic chest infection was increased by side effects of some drugs which patients take, such as Antibiotics (39 cases = 65 %), followed by steroids (20 cases = 33.33 %), while the lowest rate recorded for immunosuppressive therapies (1 cases = 1.67 %), as recorded in Table (3).

Table 1: Distribution of mycotic pulmonary infection among different chest diseases in the present survey:

Disease	No. of cases	Percentage (%)
Asthma	20	33.33
Bronchiectasis	10	16.67
Chronic Obstructive Pulmonary disease	20	33.33
ILD	1	1.67
Pneumonia	5	8.33
Tuberculosis	4	6.67
Total	60	100

Table 2: Symptoms accompanying the mycotic pulmonary infection in the present survey:

Symptom	No. of cases	Percentage (%)
Cough	60	100
Expectoration	50	83.3
Dyspnea	60	100
Chest pain	20	33.3
Hemoptysis	10	16.7
Wheeze	30	50
Constitutional symptoms	40	66.7

Table 3: Previous medication problems of patients with mycotic pulmonary infection in the present survey:

Medication problems	No. of cases	Percentage (%)
Antibiotic abuse	39	65
Steroid abuse	20	33.3
Immunosuppressive medications	1	1.67
Total	60	100

Table (4) revealed that chronic diseases were considered as other important spreading factors, as Different types of anaemia were very common risk factors for mycotic chest infection (14 cases = 23.3 %), followed by liver diseases (8 cases = 13.3 %), malignancy (5 cases = 8.33%), renal disease and CVD (3 cases= 5 %) while the lowest rate recorded for blood disease (1 cases = 1.66 %).

Type and period of patient follow-up residence were observed as an important risk factor for spreading of mycotic pulmonary infection and increasing its severity; as table (5) recorded the average days in normal ICU conditions within 5-6 days, while the MV ranged from 2-3 days and neutropenia for 5 days.

Table 4: Medical history of patients with mycotic pulmonary infection in the present survey:

Chronic diseases	No. of cases	Percentage (%)
Different types of anaemia (DM)	14	23.3
Renal diseases	3	5
Liver disorders	8	13.3
Malignancy	5	8.3
CVD	3	5
Blood disease	1	1.67

Table 5: In-patient follow-up conditions for patients with mycotic pulmonary infection in the present survey:

Type of residence	Period of residence
Normal ICU follow-up	5-6
Mechanical ventilation	2-3
Neutropenia	5

The target patients diagnosed clinically with mycotic infection were subjected to microbial culture examination, revealing single colonies only in 2 cases, while the most common was the presence of mixed fungal growth in 58 cases, as presented in fig (1).

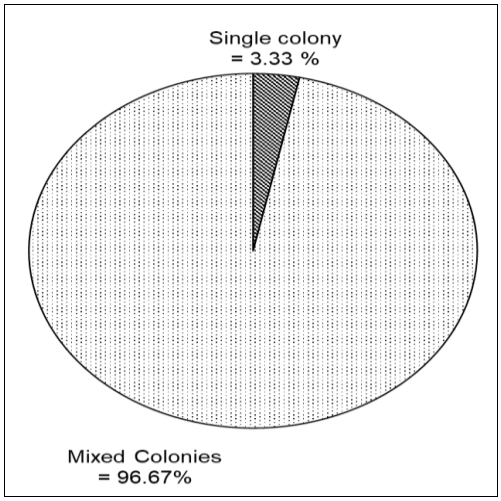

Fig 1: Microbial examination of patients with mycotic pulmonary infection in the present survey.

By identification of the collected isolates, the most common fungus was Penicillium sp. (40 %), followed by Aspergillus sp. (30 %), then both Fusarium sp. and Mucor sp. (15% for each), as shown in fig (2).

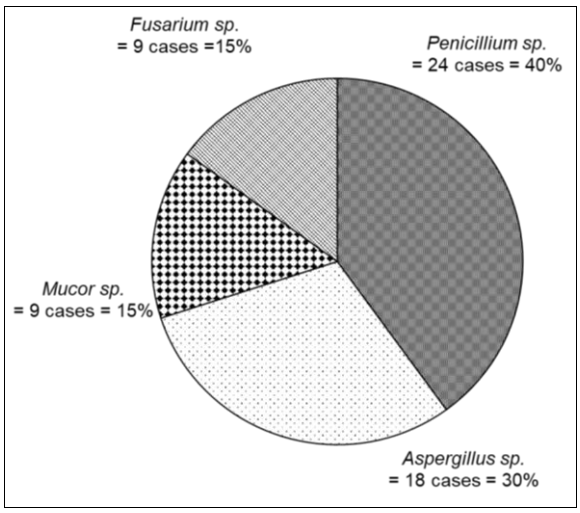

Fig 2: Frequency of different fungal isolates among the surveyed patients with mycotic pulmonary infection.

As a new trial for treatment of mycotic pulmonary infection, a comparison between natural products and commercial antifungal agents revealed a promising inhibitory effect of ethanolic extract of *Heliotropium europaeum* (a wild plant from Egyptian Halayeb and Shalateen region) with very low MIC value (25 mg/ml) against the most common fungus in the present survey (*Penicillium sp*.), compared with high MIC value (100 mg/ml) of the commercial agent (terbinafine), that was clear in fig (3).

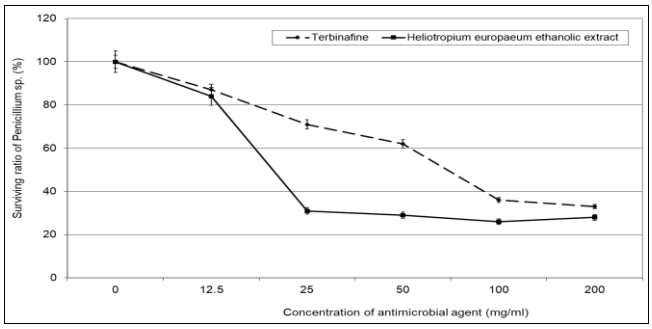

Fig 3: Comparison of antimicrobial activity (MIC) of natural plant ethanolic extract with commercial antifungal agent against the most common fungal isolate among patients with mycotic pulmonary infection in the present survey.

Discussion

The incidence of pulmonary mycosis has increased during the past few decades due to the wide use of broad-spectrum antibiotics, immunosuppressive and chemotherapy agents as well as the increased incidence of respiratory diseases, including chronic obstructive pulmonary disease (COPD), lung cancer and tuberculosis (Hsu *et al*., 2010) [5].

The highest incidence rate associated with patients suffering from Asthma and Chronic Obstructive Pulmonary disease, followed by bronchiectasis and pneumonia in the present survey. That was in agreement with another study on a group included 36patients, 35 patients and 34 patients with tuberculosis, suppurative lung diseases and pneumonia, respectively (Ahmed *et al.,* 2019) [1]. On comparing culture positivity for fungal infection among different pleuropulmonary diseases, culture-positivity rate was statistically significantly higher in COPD patients compared with pneumonia (P<0.05). Also, the culture-positive rate was statistically significantly higher in bronchial asthma patients (Ahmed *et al.,* 2019) [1].

The present records were confirmed by the highest rate of infection accompanied with cough and dyspnea, followed by expectoration, wheeze, constitutional symptoms, while the lowest rate recorded by hemoptysis. Luo *et al.* (2011) [9] in their study on pulmonary mycosis among 68 patients in China showed that the main symptoms of the patients were as follows: cough in 51 (75.0%) cases; expectoration in 38 (55.9%) cases, with blood in sputum in 18 cases, white phlegm in 12 cases, and purulent sputum in eight cases; hemoptysis in 25 (36.8%) cases; fever in 20 (29.4%) cases; chest pain and shortness of breath in five cases; headache, nausea, and vomiting in three cases. Only six (11.1%) patients were asymptomatic.

The severity of mycotic chest infection was increased by side effects of some drugs which patients take in the present study, such as Antibiotics, followed by steroids, while the lowest rate recorded for immunosuppressive therapies. The average days in normal ICU conditions were 5-6 days, while the MV ranged from 2-3 days and neutropenia for 5 days, affecting the severity of this type of infection under different residence conditions. Regarding the drugs used 83.33% of patients studied were on antibiotic therapy, 41.67% on steroid therapy and only 5% of patients used immunosuppressive drugs. About 35% of RICU patients were on MV support with a mean length of stay in ICU of about 6 days. Finally, only 5% of patients were suffering from neutropenia (Ahmed *et al*., 2019) [1].

Chronic diseases were considered as other important spreading factors for the mycotic infection under investigation in the present work, as Different types of anaemia were very common risk factors, followed by liver diseases, malignancy, renal disease and CVD. Another study by Ahmed *et al*. (2019) [1] recorded a significant association of DM with *Candida* infection, while the other comorbidities including cardiovascular, liver, renal diseases, and malignancies showed insignificant association with either *Candida* or *Aspergillus* infection.

The target patients diagnosed clinically with mycotic infection possessed single colonies only in 2 cases, while the most common was the presence of mixed fungal growth; among which the most common fungus was *Penicillium sp*., followed by *Aspergillus sp*., then both *Fusarium sp*. and *Mucor sp*. Our results came in accordance with the Farghaly *et al*. (2016) [4] study in which the major fungal species encountered in 114 (46.3%) cases were *Candida species* followed by *Aspergillus species* in 82 (33.3%) cases, *Penicillium species* in 10 (4.1%) cases, and *Fusarium spp*.

A promising inhibitory effect of ethanolic extract of *Heliotropium europaeum* (a wild plant from Egyptian Halayeb and Shalateen region) with very low MIC against *Penicillium sp*., compared with other commercial agents. Many studies on *H. europaeum* recorded a wide variety of biological activities, including antibacterial, antifungal, antitumor, anti-inflammatory, insecticidal, antispasmodic, cholagogue, emmenagogue, antipyretic, and anthelmintic effects and is used externally to treat warts and to promote wound healing (Qureshi *et al.,* 2010 [14]; Mahmood *et al*., 2011) [10].

Conclusion:
Mycotic pulmonary infection was considered a severe challenge for human health, as it possessed increasing rates with many predisposing factors and vigorous causative agents. The present study recorded *Penicillium sp.* as the most common fungus among patients with asthma, cough, DM and antibiotic abuse. That could be promisely inhibited by ethanolic *Heliotropium europaeum* extract as a new natural remedy.

Conflict of interset
There is no conflict of interest.

Authors' contributions
This work was carried out in collaboration among all authors. Authors NR and AE designed the research plan and wrote the manuscript. Author AHE performed the experimental work. All authors read and approved the final manuscript.

Disclaimer (Artificial Intelligence)
Authors hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during writing or editing of manuscripts.

Consent
It is not applicable.

Ethical approval
The protocol of sampling and patient dealing was approved by the Research Ethics Committee, Faculty of Medicine, Tanta University, with an approval code of 36264MS320/9/23.

Competing interests
Authors have declared that no competing interests exist.

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