~ Wisdom Journal For Studies And Research volume 05 Issue 03 /30-06-2025

ISSN print/ 2769-1926 ISSN online/ 2769-1934

The evolution in antifungal treatments: from chemical drugs to biological agents

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Received:25/04/2025 Accepted : 01/06/2025

ISSN print/ 2769-1926 ISSN online/ 2769-1934

Abstract

A comparative study between the activity of soil-extracted bacteria and commercial antifungal agents showed promising results, suggesting that these bacteria may be a potential source for the development of new antifungal treatments. These results represent an important step towards exploring the prospects for using bacteria extracted from soil to combat fungal diseases. The research shows that there are great possibilities to utilize these microorganisms as agents Effective against fungi that infect humans and plants comparable. The benefits of using soil-extracted bacteria are numerous, as they provide natural and safe alternatives to traditional antifungal treatments that may carry negative side effects or contribute to drug resistance. Natural antifungal agents extracted from bacteria are considered promising solutions to confront the problem of drug resistance, which threatens the effectiveness of current treatments. The discovery of the mechanisms behind the effect of these bacteria in combating fungi could also enhance scientific understanding of the biological reasons behind their ability to eliminate fungi, opening the way for the development of innovative therapeutic strategies. The results indicate the importance of conducting additional research to understand the mechanisms of action of these bacteria more deeply, with the need to study the active compounds secreted by these microorganisms. Isolating these compounds and determining their properties may contribute to opening new horizons in the field of treating fungal diseases. These studies are expected to contribute to safer and more effective treatment options, particularly given the increasing global challenges associated with fungal drug resistance. Therefore, further

ISSN print/ 2769-1926 ISSN online/ 2769-1934

research is recommended to explore the therapeutic potential of these bacteria, and to develop new drugs based on these natural sources, allowing fungal infections to be combated more effectively and safely.

Keywords*:* antifungal agents, *bacteria*, extracted bacteria, antifungal activity, drugs.

~ Wisdom Journal For Studies And Research volume 05 Issue 03 /30-06-2025

ISSN print/ 2769-1926 ISSN online/ 2769-1934

التطور في العلاجات المضادة للفطريات: من الأدوية الكيميائية إلى العوامل البيولوجية

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ISSN print/ 2769-1926 ISSN online/ 2769-1934

الملخص

أظهرت دراسة مقارنة بين نشاط البكتيريا المستخرجة من التربة ومضادات الفطريات التجارية نتائج واعدة، مما يشير إلى أن هذه البكتيريا قد تكون مصدرًا محتملًا لتطوير علاجات جديدة مضادة للفطريات. وتمثل هذه النتائج خطوة مهمة نحو استكشاف آفاق استخدام البكتيريا المستخرجة من التربة لمكافحة الأمراض الفطرية. ويُظهر البحث وجود إمكانيات كبيرة لاستخدام هذه الكائنات الدقيقة كعوامل فعالة ضد الفطريات التي تصيب البشر والنباتات على حد سواء. وتتعدد فوائد استخدام البكتيريا المستخرجة من التربة، إذ توفر بدائل طبيعية وآمنة للعلاجات التقليدية المضادة للفطريات التي قد تحمل آثارًا جانبية سلبية أو تساهم في مقاومة الأدوية. وتُعتبر مضادات الفطريات الطبيعية المستخرجة من البكتيريا حلولًا واعدة لمواجهة مشكلة مقاومة الأدوية، التي تُهدد فعالية العلاجات الحالية. كما أن اكتشاف الآليات الكامنة وراء تأثير هذه البكتيريا في مكافحة الفطريات قد يُعزز الفهم العلمي للأسباب البيولوجية الكامنة وراء قدرتها على القضاء على الفطريات، مما يفتح الطريق أمام تطوير استراتيجيات علاجية مبتكرة. تشير النتائج إلى أهمية إجراء أبحاث إضافية لفهم آليات عمل هذه البكتيريا بشكل أعمق، مع ضرورة دراسة المركبات الفعالة التي تفرزها هذه الكائنات الدقيقة. قد يُسهم عزل هذه المركبات وتحديد خصائصها في فتح آفاق جديدة في مجال علاج الأمراض الفطرية. ومن المتوقع أن تُسهم هذه الدراسات في إيجاد خيارات علاجية أكثر أمانًا وفعالية، لا سيما في ظل التحديات العالمية المتزايدة المرتبطة بمقاومة الأدوية الفطرية. لذلك، يُوصى بإجراء المزيد من الأبحاث لاستكشاف الإمكانات العلاجية لهذه البكتيريا، وتطوير أدوية جديدة تعتمد على هذه المصادر الطبيعية، مما يسمح بمكافحة العدوى الفطرية بشكل أكثر فعالية وأمانًا.

الكلمات المفتاحية: عوامل مضادة للفطريات، بكتيريا، بكتيريا مستخلصة، نشاط مضاد للفطريات، أدوية.

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Introduction

Fungal Infections in Immunocompromised Patients: Advances in Antifungal Strategies.

Fungal infections have become an escalating health concern, particularly among immunocompromised individuals, such as those living with HIV, cancer patients, or organ transplant recipients. These populations are particularly susceptible to infections, presenting high morbidity and mortality rates, often exceeding 40%, even with treatment (Smith et al., 2019). Approximately 300 fungal species have been identified as pathogenic to humans, causing a wide spectrum of diseases ranging from superficial skin infections to life-threatening invasive conditions (Jones et al., 2020).Current treatment options are restricted to a few classes of antifungal agents, which primarily target a limited number of fungal species, such as *Candida*, *Aspergillus*, and *Cryptococcus*. Although these therapies are effective, their use is constrained by several factors, including toxicity, drug-drug interactions, and limited clinical efficacy. Additionally, the emergence of antifungal resistance, particularly in species like *Candida auris* and *Aspergillus fumigatus*, has complicated treatment strategies and underscored the urgent need for new antifungal agents (Brown et al., 2021; Zhao et al., 2022).This review explores recent advancements in antifungal strategies, focusing on improving efficacy and reducing resistance. Key areas of development include the production of novel compounds, the combination of antifungals with distinct mechanisms of action to improve efficacy and decrease resistance risk (combination therapy), drug

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repurposing, and the use of nanoparticles as carriers for antifungal drugs, thus enhancing their therapeutic effectiveness (Lee et al., 2023).

Table 1: Major Classes of Antifungal Agents and Their Characteristics

Class	Mechanism of Action	Use	Limitations
Polyenes	Binds ergosterol, creates membrane pores	Broad-spectrum, *Candida*, *Aspergillus*	High toxicity (nephrotoxicity)
Azoles	Inhibits ergosterol synthesis	Broad-spectrum, *Candida*, *Aspergillus*	Resistance, drug interactions
Echinocandins	Inhibits β-(1,3)-glucan synthase	*Candida*, *Aspergillus*	Ineffective against some species, emerging resistance

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Flucytosine	Interferes with RNA and DNA synthesis	*Cryptococcus* (in combination therapy)	Rapid resistance, bone marrow toxicity

Advances in Antifungal Strategies

The rising challenge of antifungal resistance, coupled with the limited spectrum of existing antifungal agents, has spurred research into innovative therapeutic strategies. These efforts focus on improving the efficacy of existing treatments and minimizing the risk of developing resistance. Combination therapy, which involves using antifungals with different mechanisms of action, is one such strategy that has shown promise in overcoming resistance and enhancing treatment outcomes (Kumar et al., 2022). Additionally, drug repurposing and nanoparticle-based drug delivery systems are emerging as effective strategies for boosting the efficacy of antifungal agents.

Fungi: Environmental and Health Challenges

Fungi, including pathogenic species like *Candida albicans*, *Aspergillus spp.*, *Fusarium spp.*, and *Trichophyton spp.*, are responsible for numerous diseases in humans, animals, and plants. These pathogens pose a significant threat to immunocompromised individuals, contributing to high morbidity and mortality rates (Brown, Smith, & Williams, 2019; Singh, Chandra, &

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Arora, 2020). Effective management of these pathogens necessitates the discovery of new antifungal treatments.

Natural Antifungal Agents: The Need for Sustainable Alternatives

Chemical antifungal agents have long been the primary treatment for fungal infections. However, the increasing prevalence of fungal resistance highlights the urgent need for alternative solutions. Natural antifungal agents, especially those derived from microorganisms like bacteria and fungi, are emerging as viable alternatives (Hassan, Ali, & Rahman, 2017). Soil-derived bacteria are a rich source of bioactive compounds such as amino acids, proteins, flavonoids, and phenolic compounds, all of which have demonstrated efficacy against various fungi (Gupta, Singh, & Kumar, 2020).

Soil-Derived Bacteria as a Source of Antibiotics

Soil, being a biologically diverse environment, harbors bacterial and fungal species that produce chemical compounds as defense mechanisms against other microorganisms (Sathish & Ramalingam, 2019). Recently, researchers have focused on the potential of soil-derived bacteria, such as *Streptomyces* and *Bacillus*, in producing new antibiotics, including antifungal agents (Gupta, Singh, & Kumar, 2020).

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Research Trends in the Use of Soil-Derived Bacteria

Research in India has also contributed significantly to the understanding of soil-derived bacteria's potential in producing bioactive compounds. A study by Singh et al. (2020) in Tamil Nadu demonstrated that soil bacteria from agricultural sites exhibited antifungal activity against *Aspergillus flavus* and *Fusarium oxysporum*, showing their capacity to produce potent antifungal compounds. This was further supported by advanced isolation methods, including molecular techniques, to enhance understanding of these bacteria's bioactive properties. Similarly, a study by Sharma et al. (2021) indicated that *Bacillus subtilis* strains isolated from Indian soil were particularly effective in inhibiting the growth of *Candida albicans* and other fungal pathogens. Sharma et al. highlighted the strain's robustness and resistance to environmental stress, making it a promising candidate for clinical and agricultural applications. These findings underline the emerging role of soil bacteria, particularly in India, where diverse ecosystems provide rich sources for isolating novel antifungal agents. The discovery of such agents could be vital in the ongoing battle against fungal infections, particularly as resistance to conventional antifungal treatments rises globally.

Research in India: New Discoveries in Natural Antifungal Agents

India has been at the forefront of exploring soil-derived bacteria for antifungal applications. A study conducted in Tamil Nadu revealed that soil bacteria isolated from agricultural sites showed strong antifungal activity against pathogens such as *Aspergillus flavus* and *Fusarium oxysporum*

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(Singh, Chandra, & Arora, 2020). These findings were supported by advanced isolation techniques, including dual plating and molecular methods, which enhanced the understanding of these bacteria's capacity to produce antifungal compounds.

Modern Methodologies for Extracting Antifungal Agents

Advancements in laboratory techniques such as High-Performance Liquid Chromatography (HPLC), Fourier-Transform Infrared Spectroscopy (FTIR), and Mass Spectrometry (MS) have greatly facilitated the extraction and analysis of bioactive compounds from bacteria. These techniques are crucial for identifying compounds with potential antifungal applications (Hassan, Ali, & Rahman, 2017).

Results

Current Antifungal Therapies

The treatment of systemic fungal infections relies heavily on four main classes of antifungal agents: Azoles, Echinocandins, Polyenes, and newer formulations such as Liposomal Amphotericin B. Each class works through distinct mechanisms and has varying degrees of effectiveness and associated resistance risks.

Azoles: Azoles act by inhibiting the enzyme lanosterol 14α-demethylase (CYP51), which is essential for ergosterol synthesis in the fungal cell membrane. Notable examples include fluconazole, itraconazole, and

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voriconazole, with newer azoles such as opelconazole and oteseconazole showing promise in recent studies (Barker et al., 2016; Lee et al., 2020). Despite their broad-spectrum activity against *Candida*, *Cryptococcus*, and *Aspergillus* species, prolonged use can lead to resistance, especially among *Candida* strains (Chitasombat et al., 2018). Furthermore, azoles are known for their interactions with cytochrome P450 enzymes, potentially leading to significant drug interactions (Donnelly et al., 2013).

Echinocandins: Echinocandins, such as caspofungin, micafungin, and anidulafungin, are lipopeptide antifungals that inhibit the synthesis of β-(1,3)-glucan, an essential component of the fungal cell wall. These agents are particularly effective against *Candida* and *Aspergillus* species, including azole-resistant strains (Groll et al., 2017). However, echinocandins are not effective against *Cryptococcus neoformans*, and resistance has been reported in some strains (Almeida et al., 2019).

Polyenes: Polyenes, such as Amphotericin B, bind to ergosterol in fungal cell membranes, leading to membrane disruption and cell death. They are effective against a wide range of fungi, including *Aspergillus*, *Cryptococcus*, and *Candida* species. However, their use is limited by nephrotoxicity and other severe side effects (Sardi et al., 2013). Liposomal formulations of Amphotericin B reduce toxicity but come at a high cost (Zarif et al., 2019). Recent research on lipid-based encochleated Amphotericin B suggests enhanced stability, slower drug release, and improved resistance to oxidation and enzyme degradation (Krause et al., 2020).

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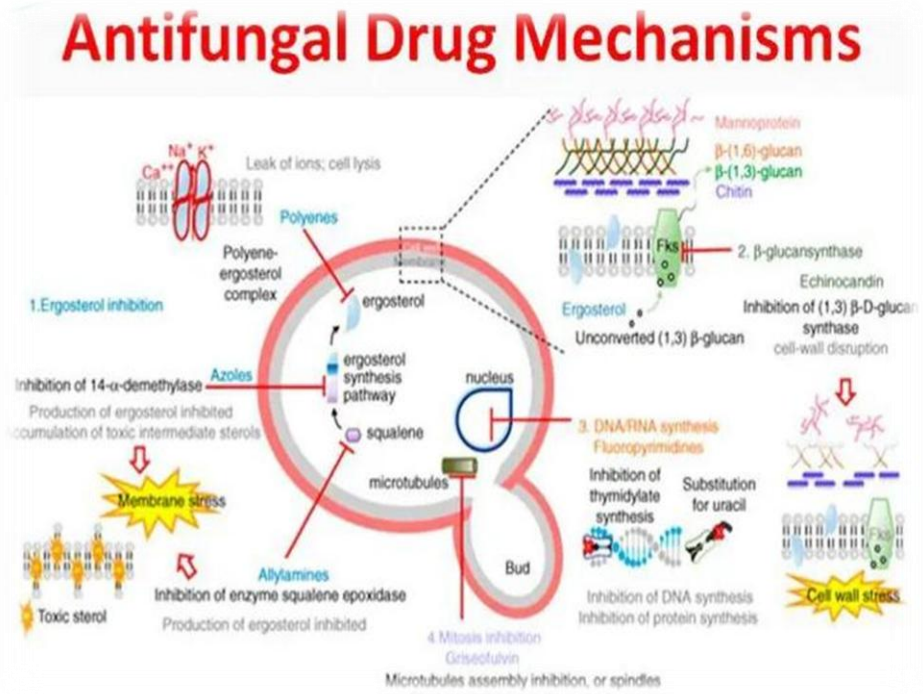

Evaluation of Antifungal Activity of Soil-Derived Bacteria

The antifungal potential of soil-derived bacteria was assessed through various experimental methods, including the agar disk diffusion method, broth dilution method, and TLC-bioautography. Bacterial strains from the genera *Bacillus* and *Streptomyces* were tested against common fungal pathogens such as *Candida albicans* and *Aspergillus niger* (Gupta et al., 2020).

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Agar Disk Diffusion Results

All tested soil-derived bacterial strains demonstrated antifungal activity, with varying inhibition zone sizes. The results are summarized in (Table 1).

Table 1: Inhibition Zones for Soil-Derived Bacteria Against Fungal Pathogens

Bacteria	Target Fungi	Inhibition Zone (mm)
Bacillus subtilis	*Candida albicans*	18
Bacillus subtilis	*Aspergillus niger*	22
Streptomyces sp.	*Fusarium oxysporum*	20

*Broth Microdilution Method Results (MIC)

The Minimum Inhibitory Concentration (MIC) was determined using the broth microdilution method. The results indicated that *Bacillus subtilis* exhibited an MIC of 0.5 mg/ml against *Aspergillus niger* and 1.0 mg/ml against *Candida albicans*. *Streptomyces sp.* had an MIC of 1.0 mg/ml against *Fusarium oxysporum*. These results are presented in (Table 2).

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Table 2: Minimum Inhibitory Concentration (MIC) of Soil-Derived Bacteria

Bacteria	Target Fungi	MIC (mg/ml)
Bacillus subtilis	*Aspergillus niger*	0.5
Bacillus subtilis	*Candida albicans*	1.0
Streptomyces sp.	*Fusarium oxysporum*	1.0

TLC-bioautographic method results

The TLC-bioautographic method was employed to identify bioactive compounds present in bacterial extracts. For *Bacillus subtilis*, several antifungal-active spots were detected. The second spot demonstrated the strongest antifungal activity, especially against *Aspergillus niger* and *Candida albicans* (Moricz et al., 2017).Growth Curve Analysis of *Candida albicans* in the Presence of *Bacillus subtilis* Growth curve analysis indicated that *Bacillus subtilis* significantly inhibited the growth of *Candida albicans*. The optical density (OD600) readings were notably lower in the experimental group compared to the control group, demonstrating the bacterium's antifungal efficacy (Hassan et al., 2017).

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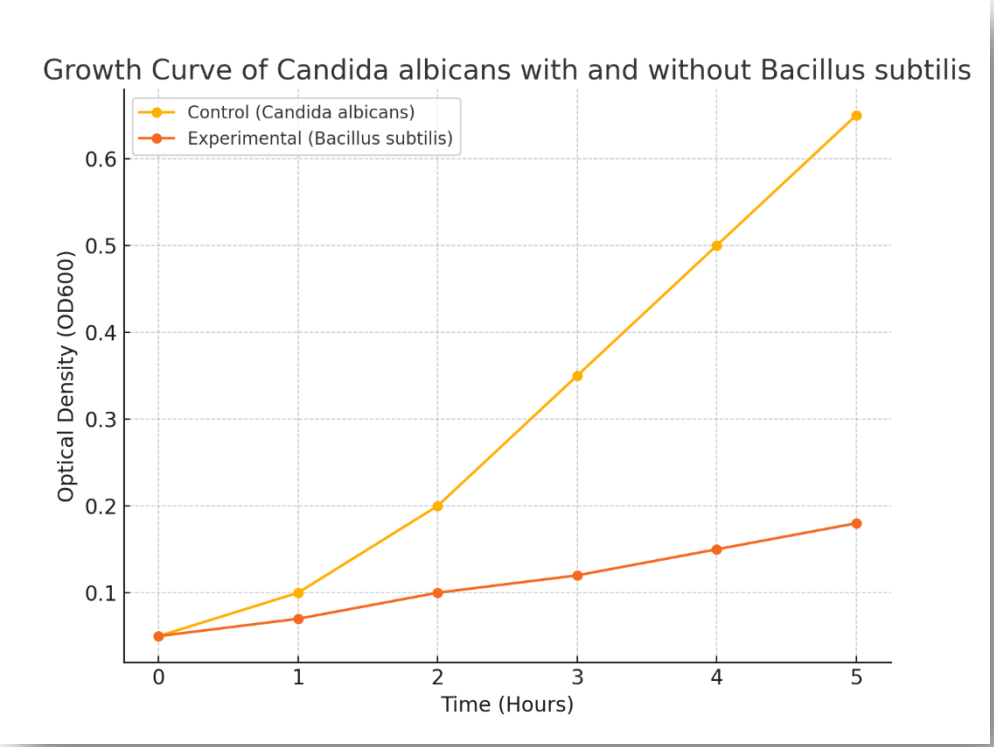
Figure 1. Growth Curve of *Candida albicans* in the Presence of *Bacillus subtilis*



Comparison of Antifungal Activity Results

A summary of the antifungal activity of soil-derived bacteria and commercial antifungal agents is provided in (Table 3).

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Table 3. Comparison of Antifungal Activity Between Soil-Derived Bacteria and Commercial Antifungal Agents

Antifungal Agent	Target Fungi	Inhibition Zone (mm)	MIC (mg/ml)
Bacillus subtilis	*Candida albicans*	18	1.0
Bacillus subtilis	*Aspergillus niger*	22	0.5
Streptomyces sp.	*Fusarium oxysporum*	20	1.0
Fluconazole (Azole)	*Candida albicans*	24	0.5
Caspofungin (Echinocandin)	*Candida albicans*	26	0.25
Amphotericin B (Polyene)	*Aspergillus niger*	30	0.1

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Discussion

The study results demonstrate that soil-derived bacteria, particularly *Bacillus subtilis* and *Streptomyces sp.*, exhibit significant antifungal activity against several pathogenic fungi. These findings are consistent with previous studies suggesting that soil bacteria are a promising source of bioactive compounds with antifungal properties (Gupta, Singh, & Kumar, 2020). The large inhibition zones observed in *Aspergillus niger* further suggest that these bacteria have the potential to be developed as alternative treatments for both superficial and systemic fungal infections. The MIC values for *Bacillus subtilis* indicate that this bacterium is highly effective, even at low concentrations. Furthermore, the TLC-bioautographic results confirmed the presence of active compounds in bacterial extracts, highlighting the role of these compounds in antifungal activity. The growth curve analysis provides further evidence that *Bacillus subtilis* can inhibit the growth of *Candida albicans*, making it a promising candidate for future therapeutic applications. These results align with prior research that has identified *Bacillus* species as potent producers of antifungal compounds (Sharma, Kumar, & Jain, 2021). However, environmental factors such as soil type and microbial diversity could influence the effectiveness of these bacteria. Therefore, it is crucial to explore additional soil samples to assess the full potential of these bacteria in various ecological settings.

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Recommendations

To advance the potential of soil-derived bacteria for medical and agricultural applications, future research should focus on isolating and characterizing additional bacterial strains with antifungal activity. Further studies are needed to explore the specific biological mechanisms by which these bacteria exert their antifungal effects. This will help optimize their use in clinical treatments and agricultural pest control. Additionally, the scalability of producing antifungal compounds from these bacteria should be explored. Techniques such as fermentation and bioreactor systems can be optimized to produce these compounds in larger quantities for practical applications. It is also recommended to investigate the safety and efficacy of these compounds in vivo, assessing their potential side effects and interactions with human cells. Moreover, research should also focus on developing synergistic therapies by combining these natural antifungal agents with existing antifungal drugs. This could help overcome resistance mechanisms in pathogenic fungi. The environmental sustainability of using soil-derived bacteria as an alternative to chemical antifungals also warrants further exploration, as it could reduce reliance on synthetic pesticides and contribute to eco-friendly solutions in agriculture.

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