European Journal of Clinical Pharmacy
Print ISSN: 2385-409X **Online ISSN**: 3105-0409
Website: https://farmclin.com/

Original Research Article

Molecular evaluation of secondary metabolites of bacteria isolated from soil using HRMS technique and determining their activity as antifungal agents

Article History:

Received: 13-11-2025
Revised: 18-11-2025
Accepted: 16-12-2025
Published: 30-12-2025

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Abstract: ***Background:*** Adolescent depression is a growing global concern, often underdiagnosed and undertreated. Cognitive Behavioral Therapy (CBT) is a well-established psychological intervention; however, its digital adaptation—Digital Cognitive Behavioral Therapy (dCBT)—offers the potential for greater accessibility and engagement. This study aimed to evaluate the effectiveness of dCBT in reducing depressive symptoms among adolescents compared to standard care. ***Materials and Methods***: A randomized controlled trial was conducted involving 120 adolescents aged 13–18 years diagnosed with moderate to severe depression using the PHQ-9 scale. Participants were randomly allocated into two groups: the intervention group (n = 60) received an 8-week dCBT program via a mobile application, while the control group (n = 60) received standard school counseling. Depression severity was assessed at baseline and post-intervention using PHQ-9 and Beck Depression Inventory-II (BDI-II). Secondary outcomes included changes in anxiety (GAD-7) and quality of life (KIDSCREEN-27). Data were analyzed using paired and unpaired t-tests, with a significance level set at $p < 0.05$. ***Results:*** The intervention group showed a statistically significant reduction in PHQ-9 scores from a mean of 15.2 ± 2.3 at baseline to 7.8 ± 1.9 post-intervention ($p < 0.001$), whereas the control group showed a smaller reduction from 14.9 ± 2.6 to 12.4 ± 2.1 ($p = 0.04$). Similarly, BDI-II scores in the dCBT group dropped from 27.1 ± 4.8 to 13.5 ± 3.2. Improvement in anxiety and quality of life scores was also significantly greater in the intervention group compared to controls ($p < 0.01$). ***Conclusion:*** Digital CBT is a highly effective intervention for reducing depressive symptoms in adolescents, outperforming standard counseling in both primary and secondary outcomes. Its scalability and accessibility make it a promising tool for broader implementation in school and community mental health settings.

Keywords: Digital CBT, adolescent depression, randomized controlled trial, PHQ-9, mental health intervention, mobile therapy, school counselling.

INTRODUCTION

From this purpose, the present study has found the main reasons that have led to a growing interest in naturals used as agents against some pathogenic microorganisms like fungi: one of the most widespread kind of microorganism and able to damage human, animal and plants. They also have effects that upend the environment. It has been reported that soil-originated bacteria have become valuable reservoirs of bioactive compounds, especially as a consequence of growing antimicrobial resistance (Dror et al., 2020; Elshafie et al., 2023). We isolated several microbes, including some which are being reported for the first time and few others which could be general microbes. from different natural environments and soil samples of Ahmadabad after laboratory investigations. Tests for new bacterial strains with special properties such as antimicrobial activity (Demis et al., 2024) are more

and more performed by researchers. Our research was grounded on the major changes connected to the environment and influenceable by environmental modifications affecting range of receptors in living organisms, e.g. in microbes which is of great significance with respect to health of living enviroment.

These modifications promote the synthesis of diverse secondary metabolites, thereby improving the microorganism's capacity to compete, resist, and endure over an extended duration.The objective of our study was to achieve multiple outcomes, including the identification of various compounds, enzymes, and secondary receptors subjected to diverse environmental conditions. Certain compounds underwent modifications, while others acquired distinctive properties. Our results demonstrated that numerous compounds, metabolites, and enzymes displayed enhanced chemical and physical stability under these adverse conditions, resulting in increased resilience to stress, humidity, and extreme temperature fluctuations. Moreover, these receptors are considered crucial for the progress and evolution of various biotechnological applications, as well as for the identification and formulation of antimicrobial agents. Our research concentrated on identifying multiple compounds that may facilitate the development of innovative antifungal agents. Our research corroborated this, emphasising the relevance of molecular analysis of secondary receptors in soil bacterial isolates, employing advanced, state-of-the-art equipment that yields accurate results. Among these instruments, high-resolution mass spectrometry (HRMS) is particularly important, as it helps identify compounds that may possess antifungal activity against resistant fungal strains.

These chemical analyses are an essential part of the diagnosis, characterisation, and identification of the structure and components of bacterial extracts. Several crucial chemical analyses have been performed to identify and characterise the essential properties of these extracts and compounds, ensuring their efficacy and suitability as safe and effective alternatives to conventional antifungal treatments (Al-Toukhi et al., 2024).

The rapid increase in antibiotic resistance among microorganisms necessitates extensive testing and investigation. The importance of these analyses stems from the growing microbial resistance, including drug and antibiotic resistance, particularly in many pathogenic fungi, which researchers consider a direct and serious threat to public health (Bhatt and Nayak, 2022). Consequently, research offers extensive insights into bacterial secondary metabolites, which signify a promising pathway for the identification of novel therapeutic agents with distinct mechanisms of action (Costa et al., 2019). These compounds, extracts, and small metabolites are known for their diversity, varied chemical structures, and potent biological activities, which make them advantageous as natural materials for developing essential antimicrobial agents. In this regard, these natural materials and bacterial extracts derived from nature have surpassed the range of synthetic organic chemicals (Chung et al., 2007).

It is composed of several antimicrobial substances that can inhibit the growth of different pathogenic microorganisms and pathogens (Santos et al., 2020). Antarctic microorganisms produce similar compounds that show strong antifungal activity against plant pathogenic fungi. This case study highlights the importance of surveying neglected areas for many years (Garcia et al., 2024). For instance, Antarctic actinomycetes. They can response powerfully against certain plant pathogens. This further demonstrates that abandoned land-- left for dead- can offer great dividends when looked at afresh and with new eyes. In general, researchers have been particularly interested in species endemic to extreme plots [11-14], mainly capable of producing novel metabolites and \aracterized by high stability and biological activity. This makes them good candidates for drug discovery (Ping et al., 2021; Syed et al., 2019). All of these new natural resources provide an appealing arena for advancing medicine, and the development of antifungal drugs from natural origin. It has wide range of antimicrobial compounds that could be used effectively in isolation to stop the growth of different plants and pathogens like fungi (Santos et al., 2020). At present, several publications have focused mainly on extremophiles that produce unique manyites with a higher biological activity and stability. This ensures they are very well suited for use as raw materials in pharmaceutical production (Ben et al., 2021; Syed et al., 2019). Several chemically pure actinomycetes isolates and strains have been isolated from the Antarctic which were active against various pathogenic fungi of plant origin, indicating that this extreme and poorly studied environment is an interesting source of microorganisms for further investigation(Santos et al., 2020). Collectively, these new resources are a precious classic one for New Antifungals.

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The aim of this study

Is to identify and characterize new antifungal compounds from naturally available bacterial sources using advanced spectrometry techniques such as HRMS to address potential pollution risks in the future.

MATERIAL AND METHODS

Materials and Instrument used for (bacterial isolation), Extraction, and Secondary Metabolite analysis.

Category	Material/Equipment	Purpose	Specifications/Grade
Culture media	Nutrient Agar	Isolation and purification of bacterial isolates	Microbiological grade
Culture media	Nutrient Broth	Enrichment of bacterial cultures and enhancement of secondary metabolite production	Microbiological grade
Solutions	Physiological saline (0.85% NaCl)	Serial dilution and preparation of bacterial suspensions	Sterile
Laboratory tools	Petri dishes, test tubes, micropipettes	Bacterial culturing and handling	Sterile
Biological material	Pure bacterial isolates	Production of secondary metabolites	Isolated from soil samples
Biological material	Pathogenic fungi	In vitro antifungal activity assays	Reference strains
Organic solvents	Ethyl acetate	Extraction of secondary metabolites	Analytical grade
Organic solvents	Methanol	Re-dissolution of extracts and sample preparation	HRMS / HPLC grade
Separation tools	Glass separatory funnel	Liquid–liquid extraction	Laboratory glassware
Equipment	Rotary evaporator	Concentration and drying of organic extracts under reduced pressure	Temperature controlled
Analytical instruments	LC–HRMS system	Qualitative analysis and molecular characterization	Equipped with ESI source
Analytical instruments	HRMS/MS	Fragmentation analysis and structural elucidation	High mass accuracy
Filtration	0.22 µm membrane filter	Filtration of samples prior to analysis	Sterile

MEHODS

MICROORGISM ISOLATION

The aim of this study is to collect soil samples to obtain new, pure bacterial isolates that have not been obtained previously.. and identified from soil samples, were enriched in nutrient broth to promote the production of secondary metabolites (Fig1). Furthermore, the authors prepared spore suspensions of the target pathogenic fungi and assessed their antifungal effectiveness (Fig. 2). Bacterial isolate cultivation and the extraction of secondary metabolites were performed using high-purity organic solvents, specifically HRMS-grade methanol. Additionally, samples were prepared for spectroscopic examination. A liquid chromatography (LC) system was integrated with the HR-MS to obtain accurate molecular data of the extracted compounds.

PREPRATION OF CRUDE BACERIAL EXRTRACT

This extract was obtained from a liquid bacterial culture using ethyl acetate in a 1:1 volumetric ratio (Figure 4). This was done by mixing thoroughly, then separating the organic phase, and then drying under reduced pressure using a rotary evaporator to obtain the crude extract (Figure 5). The extract was then stored and later reconstituted in high-purity methanol for HRMS to prepare a stock solution with a final concentration of 1 mg/mL. The solution was mixed thoroughly to ensure complete dissolution and then filtered using a 0.22 µm membrane filter before analysis. All samples were stored at 4°C until analysis.

HRMS TESTING

The High-Resolution Mass Spectrometry (HRMS) analysis of the high-resolution mass spectrometry was conducted using a mass spectrometer equipped with an electrospray ionization source. In order to detect all ionic compounds, this analysis was done in both positive and negative ionization modes. Mass spectra were collected from a satisfactory range of masses (e.g., 100-1500 m/z). The instrument was run in optimized conditions to ensure the mass was measured accurately. HRMS mass data was used to determine the elemental composition of known compounds. The first step in the identification of these substances was to make a rough comparison between data gathered and existing spectrum databases using known reference values.

RESULTS

Various bacterial isolates from the soil samples showed antifungal activity against *Candida albicans*. This activity was tested using three methods: the cross-line test, the disc diffusion method, and the cup method (Figure 2 and Figures 3A and B). The results indicate that the activity varies depending on the isolate and the method used. Isolate six exhibited the highest antifungal activity, showing a clear zone of inhibition using both the disc diffusion and cup methods. In contrast, isolate 2 showed little to no activity. This difference was also observed in the cross-line test. The cross-line test showed limited inhibition of fungal growth, and the results were inconsistent. Figures A and B show that the degree of inhibition increases from the cross-line test to the cup method, suggesting that the efficiency of the antifungal activity may vary depending on the method of assessment.

When bacterial extracts were tested in vitro using high-resolution mass spectrometry (HRMS), they showed a positive effect against Candida albicans. Secondary metabolomic analysis confirmed the presence of several novel compounds, including lipopeptides with potent antifungal activity. Structural analysis revealed that modifications to the lipid portion of these compounds enhanced their ability to disrupt fungal cell membranes, thereby increasing their biological activity. Furthermore, chemoinformatics and molecular networking based on MS/MS data facilitated the identification of known compounds and the classification of potential new metabolites, accelerating the discovery of promising antifungal agents. Reference to databases like PubChem 2.1 aided in evaluating molecular structures and comparing them with known antifungal compounds, enabling the identification of key candidate compounds suitable for pharmaceutical development (Mahmoud, 2024; Martin et al., 2019).

DISCUSSION

This discussion focuses on integrating and interpreting the findings from the discovery of novel antifungal compounds from soil bacteria and their production capabilities. The study results indicate that bacterial isolates from soil possess significant potential to inhibit "Candida albicans," growth. The test used and the bacterial isolate type affect the results evaluation. Isolate number 6 was the most effective, suggesting that it could produce a higher quantity of secondary metabolites with antifungal activity. The differences observed between the evaluation methods are primarily due to their nature and the varying sensitivity of each method to the testing site used for identifying the compounds in the medium. The spotting and cross-streaking methods showed greater efficacy. High-resolution mass spectrometry results are consistent with the presence of significant biosynthetic antimicrobial activity of the bacterial compounds. Furthermore, the cheminformatics and molecular networking tools employed proved effective in narrowing down the number of novel compounds and accelerating the discovery of new antifungal agents. The insights gained from this study underscore the therapeutic promise of microbial natural products, particularly in addressing the escalating challenge of antifungal resistance (Chen et al., 2025). Importantly, the data from this study highlights the significant therapeutic potential of natural microbial products, especially in the context of the growing problem of fungal resistance to conventional treatments. In particular, the development of novel fungal-derived peptides and lipopeptides, such as those isolated from Bacillus species, offers a promising avenue to overcome the limitations of conventional therapies due to their diverse mechanisms of action and cellular. For example, lipopeptides such as fengycins, bacillopeptins, and those produced by "Bacillus subtilis" have demonstrated potent antifungal activities by disrupting fungal cell walls and membranes (Nicoletto et al., 2024; Ramesh et al., 2024; Wang, 2021). Importantly, this complementary effect suggests the potential for developing novel multi-component antifungal agents, leading to enhanced activity and reduced resistance.

Conclusion

This study concluded that bacterial isolates obtained from soil represent a rich and promising source for the production of antifungal compounds, particularly against "Candida albicans." The results showed that certain isolates, especially isolate numbers 2 and 6, exhibited high antifungal activity across various testing through methods, indicating their potential to produce effective secondary metabolites. High-resolution mass spectrometry (HRMS) analysis confirmed the presence of new compounds, including cyclic lipopeptides with strong antifungal properties. The integration of metabolic analysis with chemoinformatics tools and molecular networking facilitated the precise identification of these compounds and in determination of their structural characteristics.

These findings underscore the importance of exploring unconventional sources of environmental microorganisms as potential sources for the development of antifungal drugs, particularly in light of increasing fungal resistance to conventional treatments. Further investigation into the precise mechanisms of action and pharmacokinetics of these compounds is warranted to fully understand their therapeutic potential and optimize their clinical application (Tarana et al., 2024). Such studies should also examine the potential for combination therapies, leveraging the synergistic effects observed among different classes of natural products to enhance antifungal efficacy and mitigate resistance development (Gharsallah et al., 2025). This approach includes exploring genetic engineering strategies to

enhance the biosynthesis of these compounds and investigating novel delivery systems to improve their bioavailability and targeted action within the host (Stancheva, 2023). Additionally, examining the influence of environmental factors on secondary metabolite production could optimize yields and facilitate industrial-scale manufacturing of these promising antifungal agents (Mahmood et al., 2023).

RECOMMENDAATIONS

This study recommends conducting in-depth future research to isolate and purify the active compounds responsible for the antifungal activity of microorganisms and to fully determine their chemical structure using advanced spectroscopic techniques.

This research explores how advanced spectroscopic techniques can be used for in-depth investigations. We also employed comprehensive bioassays for the metrical and symptomatic evaluation of the efficacy of these compounds against a wide range of fungal pathogens. We also attempted to address the toxicity of these compounds, their effects on normal cells, and their safety. To understand the molecular mechanisms inside the fungal cell environment, their biological targets must be accurately identified. This will be helpful in further understanding their chemistry. We also explored how cheminformatics or molecular modeling can be used to predict their pharmacological properties and enhance their efficacy. Finally, this research has led to increased efforts to search for novel antibacterial components with high bioavailability from diverse natural environments to further advance this research.

Figure1:show pure Bacteria isolation from soil

Figure2: show pure fungal isolation from sours

Figure 3. Show laboratory evaluation of the antifungal activity of bacterial isolates obtained from soil against *Candida albicans* using different methods. (A) shows the cup diffusion test (Cup method), (B) shows the cross-line assay.

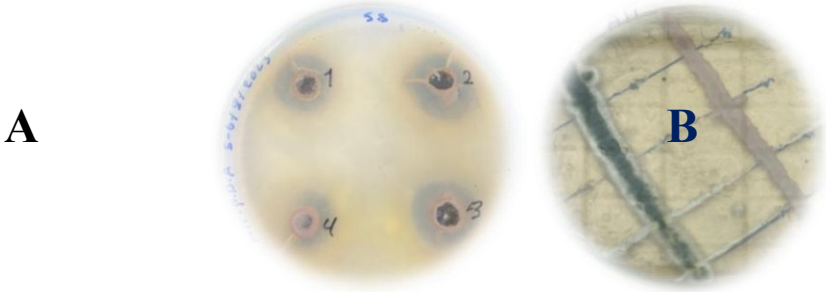


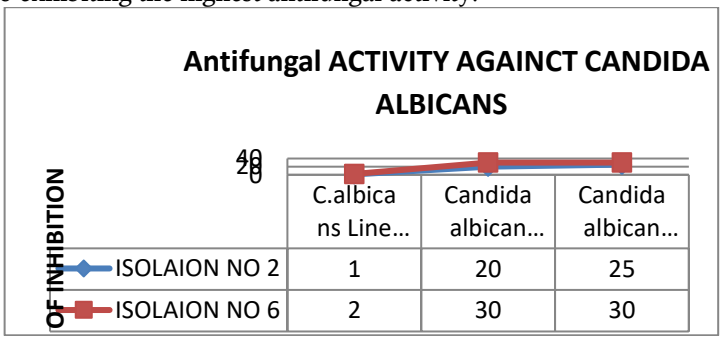
Figure4: The image shows a laboratory separators funnel containing two immiscible liquid phases.

Figure5: The rotary evaporator was used to remove the organic solvent under reduced pressure and controlled temperature, resulting in the concentration of the extract**.**

Table 2. Antifungal sensitivity by Line Cross ,disc diffusion and cup methods

S.No	Isolation No	Candida albicans (mm) Line Cross M	Candida albicans (mm) disc diffusion M	Candida albicans (mm) cup M
1	2	1	20	25
2	6	2	30	30

Curve 1. Curve plot illustrating antifungal activity of bacterial isolates against *Candida albicans* using Line Cross, Disc Diffusion, and Cup methods. The plot shows a progressive increase in inhibition zones from Line Cross to Cup method, with isolate No. 6 exhibiting the highest antifungal activity.



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