Original Article

Microbial Biosystems 10(2) (2025) 2025.366586
10.21608/mb.2025.366586.1265

Contents lists available at Egyptian Knowledge Bank
Microbial Biosystems
Journal homepage: http://mb.journals.ekb.eg/

The effect of zinc oxide nanoparticles on inhibition of *Candida albicans* isolated from leukemia patients

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ARTICLE INFO

Article history
Received 08 March 2025
Received revised 24 March 2025
Accepted 04 April 2025
Available online 01 June 2025

Corresponding Editors
Shahadha, A. I.
Al-Khafaji, Z. H.

Keywords
Antifungal,
Candida albicans,
leukemia,
metal. nanoparticles,
zinc oxide.

ABSTRACT

The use of metal oxide nanoparticles, especially zinc oxide, in medicine is crucial because of their antifungal properties as well as their physical and chemical properties. Using a biological approach, this study sought to examine the in vitro activity of zinc oxide nanoparticles against *Candida albicans* in leukemia patients. The characterization of the zinc oxide nanoparticles was done using X-ray Diffraction instrument (XRD) and Fourier transform infrared spectroscopy. The synthesized nanoparticles' capacity to suppress human *Candida albicans* isolated from leukemia patients could be accomplished by the Sabouraud Dextrose Agar technique, and they could be distinguished using the API *Candida albicans*, CHROM Candida agar, and germ tube test. Zinc oxide's antifungal properties against *Candida albicans* were examined. Fifty samples of *Candida albicans* showed resistance to fungal activity after being tested for sensitivity to several kinds of fungal antibiotics. At zinc oxide nanoparticle concentrations of 400, 200, 100, and 50 mg/ml, respectively, *Candida albicans* inhibition zones had widths of 11, 12, 12, and 10 mm; at low concentrations of 25 mg/ml, no inhibition zones were seen. This study explores the potential of green-produced zinc oxide nanoparticles as strong antifungal agents against *Candida albicans*.

Published by Arab Society for Fungal Conservation

Introduction

Leukemia is a type of cancer that primarily affects the bone marrow and blood, which are responsible for producing white blood cells (WBC). There are several different types of leukemia, which vary depending on the particular blood cell that experiences abnormal alterations and how quickly the illness progresses. Symptoms of leukemia may include fatigue, bleeding, contusions, fever, and infection susceptibility. The liver, lymph nodes, and spleen are among the organs that leukemia can affect (DiNardo et al., 2023).

Leukemia is a serious and occasionally lethal disease that requires prompt diagnosis and treatment. Treatment for leukemia differs depending on the patient's condition, stage, and kind. Among the commonly utilized treatments are targeted therapy, radiation therapy, chemotherapy, and bone marrow transplants. Nanotechnology is a new and intriguing field that can be used to deliver drugs or other compounds to specific cells or tissues. Because

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nanotechnology exclusively targets cancer cells while preserving healthy cells, it can enable leukemia treatments to be more successful and have fewer side effects (Peppas et al., 2023, Abu Rakhey et al., 2022).

Since leukemia affects people of various ages and backgrounds, it may have a big effect on society and the community. As they deal with the uncertainty, loneliness, and discomfort of the illness, leukemia patients and their families may face emotional, physical, and social difficulties. Due to the high cost and duration of treatment and aftercare, leukemia can also place a financial strain on society and the healthcare system. Additionally, leukemia can lower a patients or caregiver's quality of life and productivity (DiNardo et al., 2023).

In leukemia patients, the bone marrow produces a patient with leukemia produces a lot of aberrant white blood cells in their bone marrow (Kantarjian et al., 2021). Acute lymphoblastic leukemia makes up 75% of all instances of leukemia, a common malignancy in young adults. Due to immunosuppression brought on by illness and therapy, these kids are more vulnerable to bacterial and fungal infections as well as the reactivation of viral illnesses (Rehman et al., 2018).

Generally speaking, Candida species are benign yeasts that coexist with healthy people in a mutually beneficial relationship. Nonetheless, in immunocompromised people, they may result in infections all throughout the body (Sayed et al., 2021, Griggio et al., 2020). The human body's digestive, respiratory, and female reproductive systems, as well as the skin, are home to the yeast *C. albicans* (Talapko et al., 2021). A large percentage of superficial or invasive nosocomial infections are caused by the common fungal pathogen *C. albicans* (Kunyeit et al., 2020, Ojo et al., 2024). A mortality rate of 40% has been linked *to C. albicans* candidiasis (Hasan et al., 2024). It is easy to grow *C. albicans* in the lab, and it may be investigated both in vitro and in vivo (Gong et al., 2019).

Conversely, nanotechnology is the scientific study of materials at the nanoscale, encompassing the analysis and characterization of materials with dimensions less than 100 nm, including fibers, particles, and grains (Griggio et al., 2020). Depending on their dimensions, nanomaterial are classified as zero, one, two, or three dimensional (Nersisyan et al., 2017).

The properties of nanoparticles differ from those of similar atoms joined to form bulk materials and nanoparticles, which are bigger than atoms and molecules but smaller than bulk materials (Reier et al., 2012, Al hamza Hasoon et al., 2024). Materials at the nanoscale behave differently from those at the macroscopic level. Numerous methods, such as precipitation, chemical vapor deposition, hydrothermal synthesis, milling, etching, sputtering, and laser ablation (Mohammed et al., 2024, Sami et al., 2024, Sheltagh et al., 2024), have been used to create nanomaterial. These techniques have been used to benefit from nanoparticles' higher surface-to-volume ratio than those of bulk materials. Furthermore, the production of nanomaterial has also made use of biological methods, including plants and microorganisms (H N.2023).

One important type of metal oxide nanoparticles is thought to be ZnO NPs. As an inorganic material, zinc oxide nanoparticles have unique properties with an energy gap of 3.37 electron volts and a white, insoluble powder appearance at typical outside temperature (Azmana et al., 2021, Barakat 2019). They have been used in many different industries, in addition to industrial (rubber, concrete, and textile) and biological (antibacterial and antifungal) applications (Saeed & Saadullah 2019; Jasim et al., 2023).

A significant public health challenge is the increasing prevalence of fungal infections, namely those brought on by *C. albicans*. Traditional antifungal medications frequently have drawbacks, such as the emergence of resistance and unfavorable side effects. In this regard, the demand for creative and long-lasting methods to treat fungal infections is increasing. An interesting approach that uses eco-friendly techniques to strengthen the antifungal toolbox is the biosynthesis of ZnO NPs.

The development of novel therapeutic strategies in the field of nanomedicine depends on our ability to comprehend the effects of these zinc oxide nanoparticles, which were synthesized in an environmentally friendly manner, on *C. albicans*. In this biological investigation, we intend to investigate if zinc oxide nanoparticles are effective against *C. albicans* in vitro in patients with leukemia. The antifungal efficacy of zinc oxide nanoparticles synthesized utilizing eco-friendly methods against *C. albicans* has been thoroughly evaluated through clinical trials. *C. albicans* is a harmful pathogen for humans and animals (DiNardo et al., 2023). Zinc oxide nanoparticles (ZnO NPs) and other nanomaterial have been criticized for their peculiar biological, chemical, and physical properties. Studies show that zinc oxide, silver, gold, copper oxide, and iron oxide nanomaterial are antifungal. ZnO NPs are promising agents because to their surface attraction and physiochemical stability (Peppas et al., 2023).

Alternative antifungal medicines are required to combat multi-drug-resistant fungus. Zinc oxide nanoparticles (ZnO NPs) have garnered global interest owing to their varied shape, substantial surface area to volume ratio, biocompatibility, extensive antibacterial and antifungal properties, reduced susceptibility to resistance development, and environmental safety (Srivastava et al. 2021). ZnO NPs are also important in gas sensors, biosensors, cosmetics, and drug-delivery systems, as they

possess antimicrobial properties (DiNardo et al., 2023, Peppas et al., 2023).

The objective of this study was to evaluate the in vitro antifungal activity of biologically synthesized zinc oxide nanoparticles against *Candida albicans* isolated from leukemia patients, and to assess their potential as effective antifungal agents.

Materials and Methods

Samples collection.

Fifty swabs were taken from hospitalized adults receiving chemotherapy for acute leukemia who had oral thrush, oral ulceration, microsites, mucosal ulceration, and white plaques. These swabs were then cultured on SDA and differentiated using the CHROM candida agar test, the germ tube test, and API candida.

Germ Tube test (GTT)

This test is a rapid method of differentiating Candida albicans from other species because it may develop small germ tubes after two hours of incubation in human blood serum at 37 °C. Germ tubes are extensions of the daughter cells of the mother cell, as opposed to pseudo hyphae, which go through origin-based contractions (Ezz et al., 2023).

CHROM agar

All Candida colonies on Sabouraud Dextrose Agar (SDA) and Potato Dextrose Agar (PDA) were sub-cultured by streaking a loop of culture onto CHROMO agar Candida media and incubated for 48 hours at 37 °C. This selective and differential media allows for the rapid isolation and presumed identification of various clinically relevant Candida species based on colony color and phenotype. The CHROM agar medium, as described, has a chromogenic substrate that combines with the enzymes released by Candida species to create colonies that exhibit unique coloration (Abdo et al., 2021).

Antifungal of zinc oxide nanoparticles

Using a specialized sterile borer (5 mm in diameter), a small swab of the most resistant *C. albicans* sample was taken after the PDA was poured into a petri dish and evenly distributed around the PDA's surface (Hussein et al., 2024). After that, wells were created in a petri plate using the PDA surface.

In addition to deionize water as a control, 0.1 mL quantities of various concentrations of zinc oxide nanoparticles (50, 100, 200, and 400 mg/mL) were dissolved in sterilized deionized water and added to the wells. Lastly, the plates were put in the incubator for 72 hours. At 37 °C, the development of growth inhibitory zones was examined. When the growth inhibition zone developed, its diameter was measured in millimeters (mm).

Biosynthesis of ZnO NPs

The modified procedure (Pappas et al., 2003) was used in the biosynthesis of zinc oxide nanoparticles. According to the following steps:

First: take 25 ml of culture to contain bacteria *Pseudomonas putda*, and dilute with 75 ml D.W. The culture fluid was supplemented with 100 mg of Zn (NO3)2 (Sigma Aldrich).

Second: maintained at a temperature of 37°C with a rotational speed of 50 rpm. After 24 hours, a white deposition started to form at the bottom of the flask, indicating the transformation of the ion.

Third: After being allowed to incubate at room temperature, the culture fluid was cooled. The reaction mixture contained noticeable accumulations of white clusters that had settled at the flask's bottom after two days of incubation on a rotary shaker.

Fourth: the sample of broth culture was centrifuged for 15 minutes at 5000 revolutions per minute (rpm) after the incubation time. Following their separation, the pellet and supernatant fractions underwent a drying procedure. A solid powder specimen was then formed by transferring the liquid component onto a Petri plate and drying it in a hot air furnace set to 400 °C for two hours.

Materials testing using Nanotechnology

Nano characterization is the process of carefully examining and comprehending materials and structures at the nanoscale, which is often defined as having a diameter of 1 to 100 nanometers. For a variety of scientific, commercial, and technological applications, accurate characterization is crucial because the properties and behaviors of materials at this size might differ significantly from those at the macroscopic level. To do this, a variety of advanced tools and methods collectively referred to as Nano-characterization instrumentation have been created.

Scanning Electron Microscopy (SEM)

Scanning electron microscopy (SEM) is an advanced imaging method that generates high-resolution, three-dimensional pictures by scanning a specimen's surface with electrons. Taking pictures of nanoscale surfaces and structures is made much easier with its many hundred thousand times magnification. Electron microscopy (SEM) is an indispensable tool for studying nanomaterial's' topography, composition, and form (Ahmed et al., 2025).

Transmission Electron Microscopy (TEM)

Transmitting electrons through a tiny material enables atomic-scale detailed analysis, elevating TEM imaging to a new level. Nanomaterial's' crystallography, flaws, and chemical make-up can be better understood with this method (Mahdi et al., 2024).

Atomic Force Microscopy (AFM)

Applying force microscopy (AFM) involves delicately gliding a pointed tip over the surface of a specimen in order to detect the force exerted by material contact. This technique provides extremely high-resolution topographical data, which allows one to see individual atoms. Analysis with AFM has many uses. In order to study nanomaterial' surface roughness, chemical interactions, and mechanical properties (Mahdi et al., 2024).

X-ray Photoelectron Spectroscopy (XPS)

Fluorescence spectroscopy (XPS) is a surface-sensitive technique for analyzing the chemical composition and physical condition of a material. The binding energies of the atoms in a material are determined by exposing it to X-ray radiation and then analyzing the photoelectrons that are emitted. It is necessary to employ XPS in order to characterize the surface chemistry and electrical structure of nanomaterial (Mohammed et al., 2024).

Fourier Transform Infrared Spectroscopy (FTIR)

Measuring a material's infrared light absorption is done using a spectroscopic technique known as Fourier transform infrared spectroscopy (FTIR). Common applications include the detection of functional groups, molecular vibrations, and chemical bonding in nanomaterial. For the purpose of studying the molecular composition and structure of biological and organic nanomaterial, Fourier transform infrared spectroscopy (FTIR) is a powerful tool (Sami et al., 2024).

Results

Minimum Inhibitory Concentration (MIC)

In this study, the MIC for three popular antifungal medications terbinafine, itraconazole, and fluconazole was calculated using the excellent diffusion method. *C. albicans* was used to test their in-vitro sensitivity to specific antifungal medications. Table 1 shows that *C. albicans's* resistance begins at 25 ug/ml and that the MIC is 50 ug/ml. According to Hasoon et al. (2024), this study backs up their conclusions.

Terbinafine is the main agent of allylamine. Ergo sterol, an essential sterol in the plasma membrane of fungal cells, is not produced as much. Terbinafine blocks the action of the enzyme squalene epoxidase, which catalyzes the conversion of squalene into squalene-2, 3-epoxides, a precursor of lanosterol, a direct precursor of ergosterol. It can be used orally and topically (Ali et al., 2018).

Itraconazole's minimum inhibitory concentration (MIC) against *C. albicans* was found to be 25 ug/ml. Our results align with those of Stabily (Qazi et al., 2009). Belonging to the Azole family, itraconazole exhibits efficacy against a variety of pathogenic fungus, such as *Candida* and dermatophytes. When treated to fluconazole, *C. albicans* showed a minimum inhibitory concentration (MIC) of 25 ug/ml. On the other hand, studies carried out in Baghdad by (Sun et al., 2018) showed that fluconazole is useless against *Candida* species.

The antifungal spectrum of fluconazole is more limited than that of other azoles.

Table 1 Minimum Inhibitory Concentration (MIC) of three antifungal agents Against *Candida albicans*

Fungal isolate	MIC		
Candida albicans	Terbinafine (µg /ml) **50**	Iitraconazole (µg /ml) **25**	Fluconazole (µg /ml) **25**

Characterization of Zinc Oxide Nanoparticles

The reduction of Zn+ into zinc oxide nanoparticles upon exposure to *Pseudomonas putida* culture filtrate may be linked to the color shift. The culture was dark yellow when it was first filtered. Nevertheless, with the addition of Zn (NO3)2 and a 24-hour incubation period at 37°C and 50 rpm of shaking, the emulsion became white.

The color changes seen in aqueous solutions are caused by surface-Plasmon resonance, or SPR. The topography and surface morphology were determined using a scanning probe microscope. As seen in Figure -1A, the atomic force microscope (AFM) provides both two- and three-dimensional representations of the nanoparticle's surface. The average diameter of the particles was found to be in the nanoscale range. AFM-SPM was used to measure the size of zinc oxide nanoparticles, and the results show that the average size of the nanoparticles was 69 nm, as shown in (Figure 1B).

Pseudomonas putida culture filtrate-produced biologically produced nanoparticles were analyzed using an X-ray diffraction device to determine the average particle size and crystal (Fig. 2). The XRD spectrum in the image shows the zinc oxide nanoparticles that were produced using a *Pseudomonas putida* culture filtrate.

The spectrum reveals distinct peaks corresponding to crystallographic planes at 100, 002, 101, 102, 110, 103, 112, 004, and 104. These peaks appear at Bragg angles of 31.70°, 34.34°, 36.16°, 47.54°, 56.48°, 62.78°, 67.66°,

72.53°, and 76.58°, respectively, confirming the crystalline nature of the synthesized zinc oxide nanoparticles.

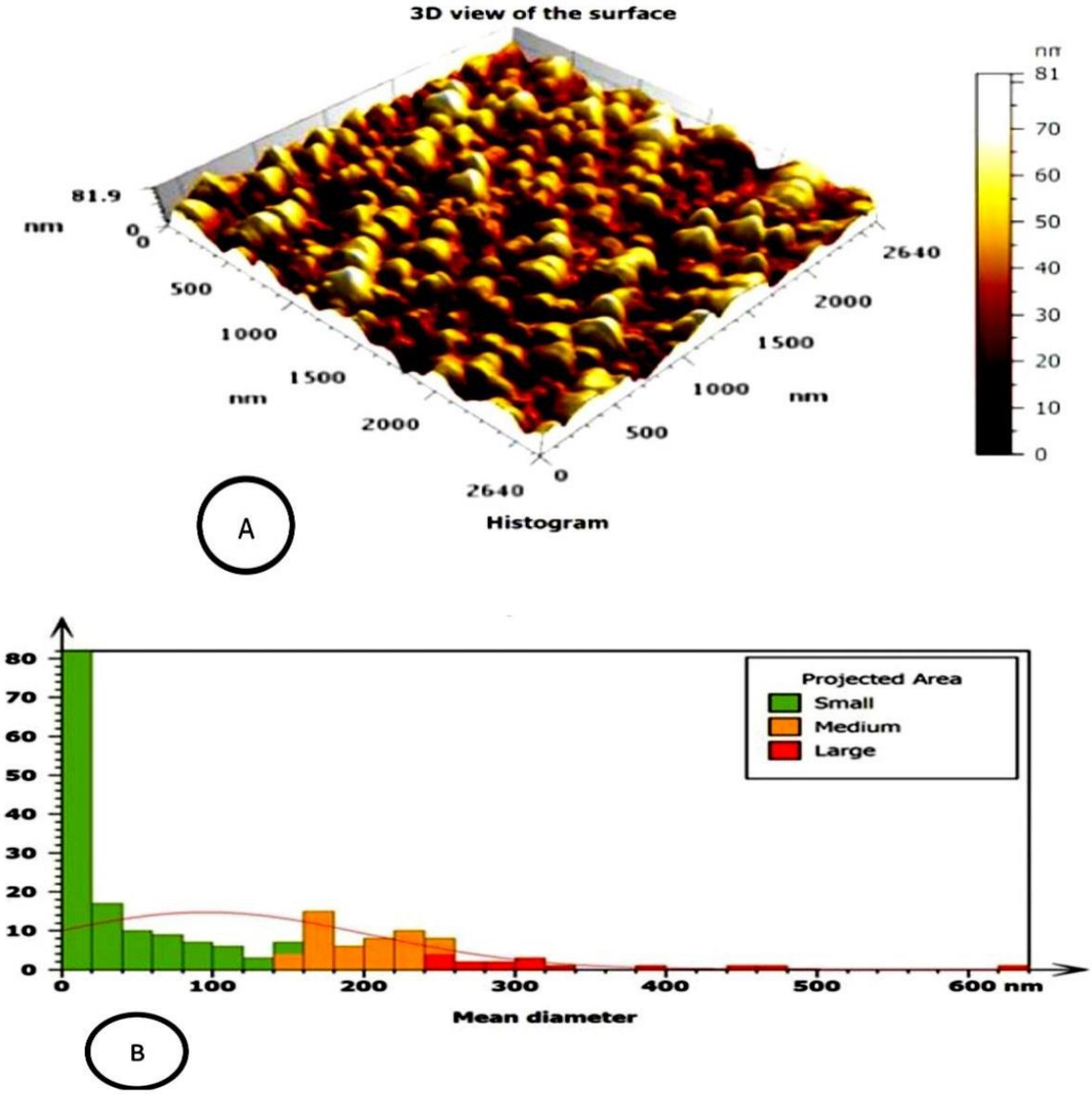

Fig 1. AFM characterization of zinc oxide nanoparticles. (A) Surface morphology, (B) Granularity distributed zinc oxide nanoparticles chart.

x

Additionally, Fourier Transform Infrared Spectroscopy (FTIR) analysis was performed to study the functional groups present (Fig. 3). The FTIR spectrum revealed two prominent peaks at 445.57 cm^{-1} and 445.58 cm^{-1}, corresponding to the characteristic vibrations of Zn–O bonds, confirming the successful synthesis of zinc oxide nanoparticles.

A weak peak observed in the region between 1500 and 1600 cm^{-1} and a strong peak at 1508.38 cm^{-1} indicate the presence of carbon-carbon bonds, which may be attributed to aromatic rings or alkane groups possibly originating from biological components involved in nanoparticle synthesis.

The agar well-diffusion technique was followed, it was designed by (Akpomie et al., 2021). However, it was used to assess the antifungal effectiveness of zinc oxide nanoparticles against Candida albicans (Fig. 4). The results showed that at a concentration of 400 µg/ml, the inhibition zone had a diameter of 18 mm, as shown in Fig. 4A. Fig. 4B illustrates the inhibition zone at 200 µg/ml, while Fig.

4C shows a 10 mm inhibition zone at 100 µg/ml. However, no inhibition zones were observed at the lower concentration of 12.5 µg/ml, as depicted in Fig. 4D. The exact chemical mechanisms underlying the antifungal properties of zinc oxide nanoparticles remain unclear.

Discussion

The MIC results support the findings of Hasan et al. (2024). Terbinafine, the main allylamine agent, reduces the production of ergosterol, an essential sterol in the plasma membrane of fungal cells. It inhibits the enzyme squalene epoxidase, which catalyzes the conversion of squalene into squalene-2, 3-epoxide, a precursor of lanosterol and ultimately ergosterol (Table 1).

Terbinafine can be administered both orally and topically (Ali et al., 2018). The minimum inhibitory concentration (MIC) of itraconazole against *Candida albicans* was found to be 25 µg/ml, consistent with the results reported by Qazi et al. (2009). As a member of the azole family, itraconazole is effective against a variety of pathogenic fungi, including *Candida* species and dermatophytes.

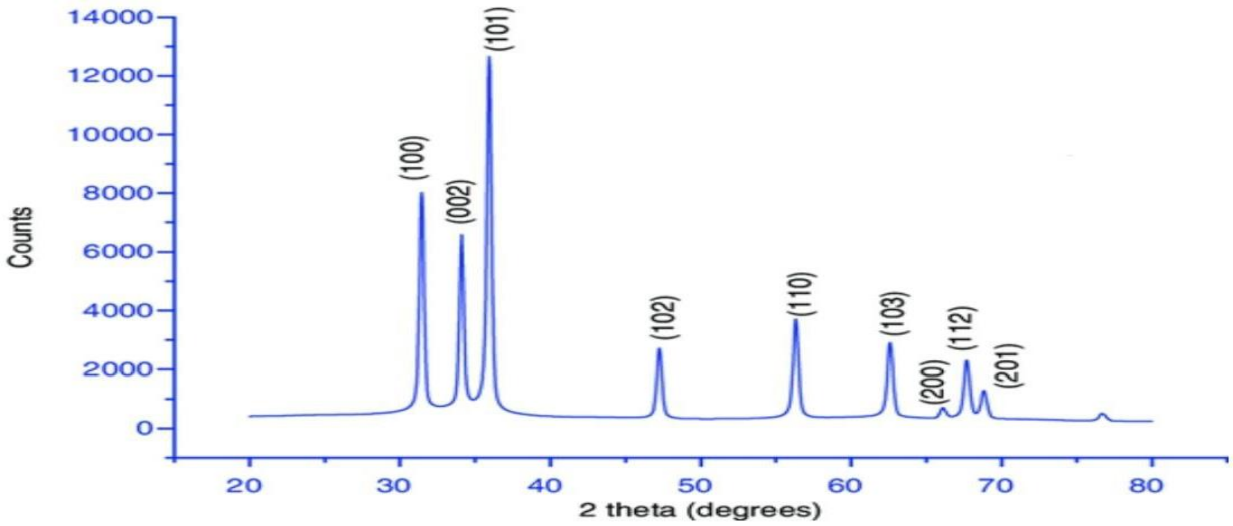

Fig 2. XRD pattern of biologically synthesized zinc oxide nanoparticles.

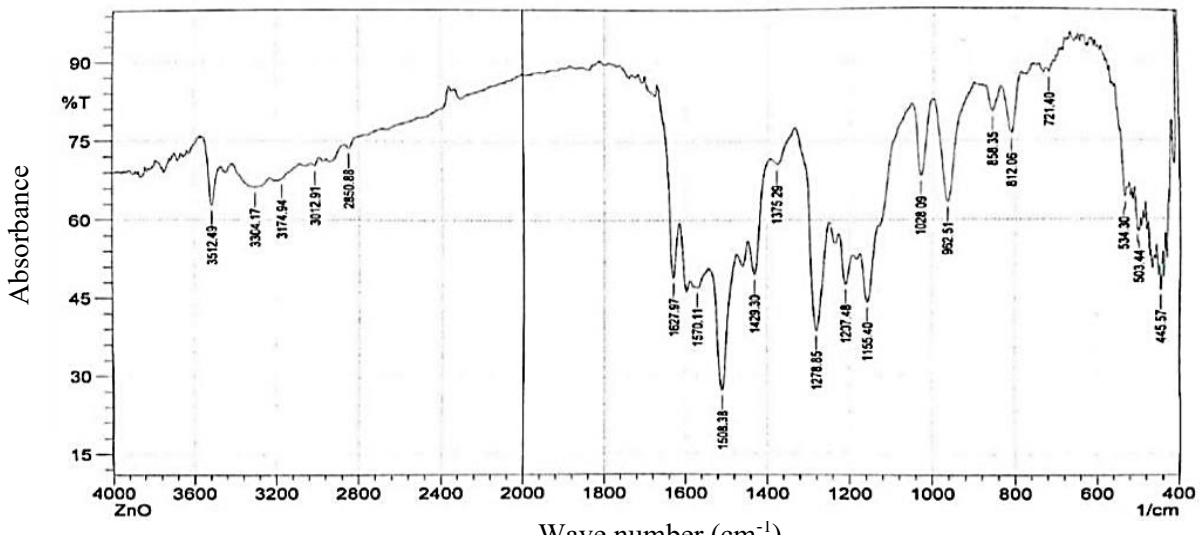

Fig 3. FTIR spectrum of biologically synthesized zinc oxide nanoparticles.

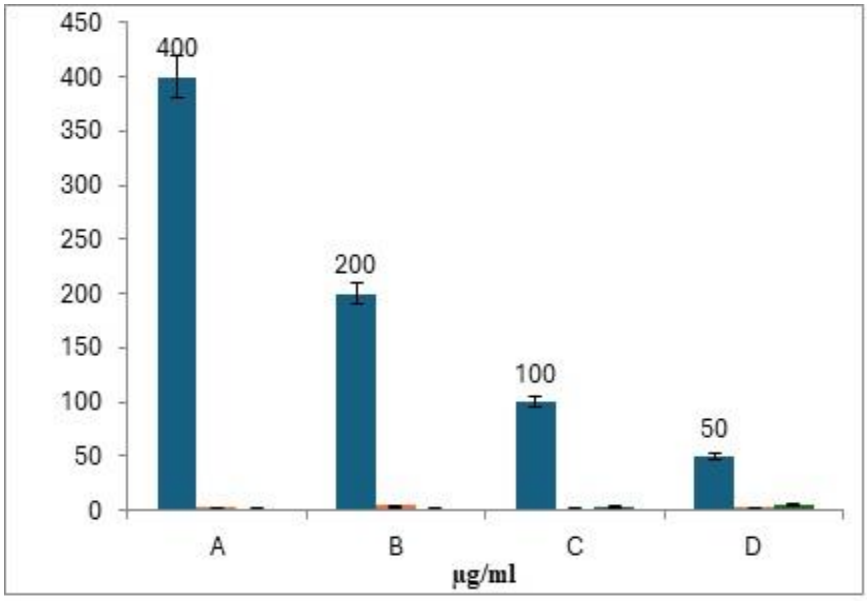

Fig 4. Antifungal susceptibility test of zinc oxide nanoparticles against Candida albicans: (A) 400 µg/ml, (B) 200 µg/ml, (C) 100 µg/ml, and (D) 50 µg/ml concentrations.

When treated with fluconazole, *Candida albicans* showed a minimum inhibitory concentration (MIC) of 25 µg/ml. However, studies conducted in Baghdad by Sun et al. (2018) indicated that fluconazole is ineffective against *Candida* species. The antifungal spectrum of fluconazole is more limited compared to other azoles (see Table 1).

The results confirm that the tested material consists of high-purity zinc oxide nanoparticles. The average size of the zinc oxide nanoparticles was found to be between 20 and 40 nm, calculated using the Debye–Scherrer equation (Salem et al., 2022).

The FTIR analysis revealed two peaks at 445.57 cm^{-1}, representing bond vibrations between oxygen and zinc molecules, which correspond to two distinct types of vibrations. Additionally, a weak peak and a strong peak at 1508.38 cm^{-1} within the range of 1500 to 1600 cm^{-1} indicate the presence of carbon-carbon groups, such as aromatic rings or alkane groups. Peaks observed between 1500 and 1700 cm^{-1} correspond to the symmetric and asymmetric stretching of carbon-oxygen groups (C–O) and a stretching mode at 2850.88 cm^{-1}. This range also indicates the bond between carbon and hydrogen (C-H), which further implies that zinc oxide nanoparticles have water molecules attached to their surfaces (Fig. 2 & 3). Several possible mechanisms were postulated to explain the antifungal effects of zinc oxide nanoparticles in this investigation. Zn^{3+} ions are released into the cell and build up in the cytoplasm when the fungal cell wall interacts with the surface of zinc oxide nanoparticles (Kunyeit et al., 2020). Fungal cells can be damaged by Zn^{2+} ions through metabolic disruption, nucleic acid aggregation, ribosome breakdown, protein alteration, and electron transport chain interruption. The permeability of the cell wall is increased due to this injury, which could cause plasma fluid and cellular components to leak out (Fig. 4).

We suggest using polymerase chain reaction (PCR) and other molecular methods to identify disease-causing microbes. The PCR technique has been utilized in numerous infectious subjects (Shehab and Al-Rubaii, 2019; Zedan and Al-Amer, 2023; Rasoul et al., 2023; Al-Rubaii, 2017; Sutan et al., 2023; Al-Khafaji, 2023; Abdulkaliq et al., 2022; Jassim et al., 2025; Al-saidi et al.,2022; Khalaf et al., 2025; Husain and Alrubaii, 2023; Muhammed et al., 2024a ; Ibrahim and Laftaah, 2024; Abdullah and Al-Rubaii, 2024; Bassi et al., 2024; Muhammed et al., 2024b; Al-Khafaji et al.,2025) and has also been applied to detect various cancer cases, including

gastrointestinal sarcoma (Zedan and Al-Amer, 2022), blood cancer (Al-Maliki and Zedan, 2024).

Conclusion

This work investigates green-synthesized zinc oxide nanoparticles as potent Candida albicans antifungals. Nanoparticle physicochemical characteristics, biological activity, and production were fully studied. Significant findings showed bioactive components from the green source increased nanoparticles' distinctive features. This study enhances nanomedicine by showing how green production produces nanoparticles with better biological activity. Future research should optimize synthesis, assess green-synthesized zinc oxide nanoparticles' in vivo efficacy, and explore their medicinal potential.

Acknowledgments

The authors are grateful to the University of Technology, Baghdad, Iraq for technical help and research equipment.
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Ethical approval

This study was approved by the local ethics committee at the University of Technology, Iraq, with reference number 235 dated 29/11/2023. In accordance with the Declaration of Helsinki, informed consent was obtained from all participants.

Conflict of Interest:

All authors declare that they have no conflict of interest.

Funding

No governmental, commercial, or nonprofit funding agencies provided any funds for this project.

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