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Antimicrobial Activity of Nanozirconium Oxide

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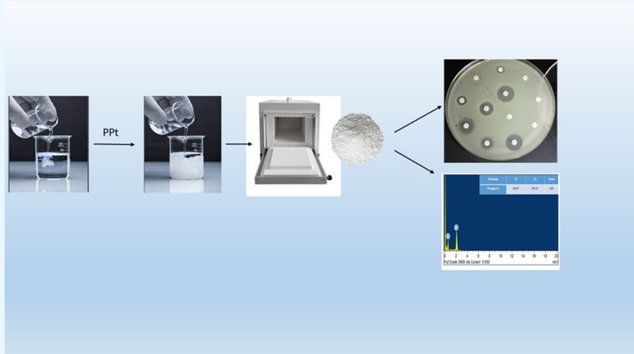
ABSTRACT: The goal behind this work is to prepare, characterize, and study the antimicrobial behavior of zirconia (ZrO_2) nanoparticles (NPs). Various techniques, such as X-ray diffraction (XRD), were used for studying the mineralogical structure and crystal size. The microstructure and chemical composition of the prepared particles were analyzed using a scanning electron microscope attached with an energy-dispersive X-ray analysis (EDAX) unit. The antagonistic ability against several Gram-negative and Gram-positive bacteria, including *Salmonella paratyphi, Pseudomonas aeruginosa, Alcaligenes aquatilis, Escherichia coli, Streptococcus pneumoniae*, and *Staphylococcus aureus*, was assessed using the well diffusion method. The results of XRD and scanning electron microscopy (SEM) analyses revealed that the prepared material exhibited the phase of zirconium nanoparticles with particle sizes ranging between 40 and 75 nm. The antimicrobial test results demonstrated that the inhibitory effect increased with the increase of concentration. The inhibitory effect was more pronounced against Gram-positive bacteria, as indicated by the larger size of the inhibitory zone. At a 9% dimethyl sulfoxide (DMSO) concentration, the inhibitory zone had a diameter of 3.50 mm for *S. aureus* compared to a diameter of 3.40 mm for *S. pneumoniae*. The use of zirconium oxide nanoparticles reduced the diameter of the inhibitory zone when tested against *S. aureus* at a 3% DMSO concentration (0.50 mm diameter) and against *S. pneumoniae* (0.40 mm diameter). Zirconia nanoparticles were also evaluated for their antifungal activity against several species, including *Aspergillus niger*, *Aspergillus flavus*, and *Penicillium* sp. The size of the inhibitory zone indicated the susceptibility of microorganisms to nanozirconium oxide, resulting in a stronger inhibition of *Penicillium* sp. at a 100% DMSO concentration (4.50 mm diameter) compared to *A. niger* and *A. flavus* (3.00 mm diameter). The results for *Penicillium* sp. at a 3% DMSO concentration showed a diameter of the inhibitory zone of 0.90 mm, while for *A. niger* and *A. flavus*, the diameter was 0.80 mm. Thus, our findings demonstrate that the zirconium oxide nanoparticles possess the capability to reduce the inhibition zone effectively for both bacterial and fungal activities.



1. INTRODUCTION

Nanotechnology developed in the twentieth century has made significant contributions and shows capabilities of achieving high degrees of accuracy in the functioning of tools used in different fields (medicine, engineering, agriculture, drugs, communications, defense, and space fields). Improvement of material properties and functionality can be achieved by doping processes and decorating methods based on the sizes and shapes of materials and their components. Nanotechnology is also defined as the science of designing, characterizing, and production and application of structures, systems, and devices by controlling their properties (shape or size) at the nanometer scale and their functionality.[1−4] The advancement and development of nanotechnology, particularly in medical fields, have contributed to and helped in prevention, diagnosis, and treatment of diseases.[5−8]

Many researchers have reported the advantages of nanotechnology in enhancing and improving the physicomechanical properties of materials using nanometer-scale materials for utilizing their excellent characteristics and functionalities, such as good mechanical strength, in production and application of electronic devices when compared to bulk materials.

Dinesh et al.[9] and many authors[10−15] revealed the advantages of nanomaterials in biotechnological and biomedical applications, such as overall improvement, excellent properties, unique size, large surface area, and biocompatibility with nanotechnology. As a new generation material, nanomaterials can be utilized for detection and treatment of diseases (such as biosensor, bioimaging), energy storage, and environ-

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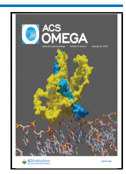

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mental science. One of these applications is in the dentistry field in which some nanoparticles, especially ZrO_2 particles, are used.

Zirconia has been utilized in pediatric dentistry since 2008 in the form of crowns.[16] Apart from its esthetically pleasing color, it exhibits a highly polished surface and exceptional durability. It also accumulates less biofilm, which contributes to better gingival health and ultimately leads to higher satisfaction among parents.[17−21] However, it necessitates extensive tooth preparation and is more expensive when compared to standard stainless-steel crowns.[17,22]

In addition to its outstanding properties, such as chemical resistance and remarkable mechanical strength, zirconia is well known for its exceptional durability. It serves as an alternative to alumina and is suitable as a biomaterial for various dental applications, including the fabrication of endodontic posts, crowns, bridge restorations, implant abutments, and other applications.[23−33]

Many efforts have been made by researchers in the dentistry field to study the application of such nanoparticles that can help in esthetics and improve the characteristics of metal oxides to avoid the concerns related to toxicity and allergic reactions to certain metal oxides or alloys that can replace titanium oxide and alumina for dental implants. They reported that zirconia can be used as an alternative metal oxide due to its capabilities and functionalities, such as osseointegration, biocompatibility, favorable soft tissue response, tooth-colored restorations, and esthetics that are required by both patients and doctors.[34]

Many authors have demonstrated the use of zirconia nanoparticles as additives and doping materials to improve and enhance the physicochemical and physicomechanical properties, including mechanical strength.[35−40] Khalil et al.[2] showed promising results in improving refractory bricks (through physicomechanical and refractory properties). They reported that the best properties were achieved with the addition of 8% zirconia nanoparticles. Aly Kamal et al.[41] calculated the stress, strain, and energy density of zirconia nanoparticles based on the Williamson−Hall (W−H) analysis using different models, and they have demonstrated the isotropic behavior of zirconia. To the best of our knowledge, there have been no reports on the biological activity of zirconia nanoparticles.

This work is different from other research work in the sense of the role of zirconium oxide being used in pediatric dentistry, and in one of the esthetic applications (shape, color and appearance, stability, and strength), these novel behaviors can be used to differentiate among other metal oxides in addition to the lower cost of the as-prepared nanoparticles when compared with other metal oxides, This study aims to investigate the antimicrobial activity of zirconium oxide (ZrO_2) nanoparticles, considering their potential importance in biomedical and healthcare applications.

2. MATERIALS AND METHODS

2.1.1. Materials. Zirconium oxychloride ($ZrOCl_2$) and a dilute solution of ammonia (i.e., 25% NH_4OH, BDH) were used for preparing the nano zirconia (ZrO_2) powder, and the details are given in ref 2.[2] Dimethyl sulfoxide (DMSO) was used as is (Sigma-Aldrich) when processing samples for antimicrobial tests.

2.1.2. Instruments. A drying oven, a muffle furnace, an X-ray diffractometer (Bruker, Germany; D8 ADVANCE), and a scanning electron microscope (JEOL JAX-840A -Japan) were used in this study.

2.1.3. Preparation of Zirconia Nanoparticles. Zirconia nanoparticles (ZrO_2) were prepared via stepwise addition of diluted (1:1) ammonia solution to 2 M zirconium oxychloride octahydrate ($ZrOCl_2$-$8H_2O$) solution using the neutralization method at pH 8.0 as mentioned in the literature[2] and shown in Figure 1. The obtained precipitate was calcined at a temperature of 900 °C for 1 h.

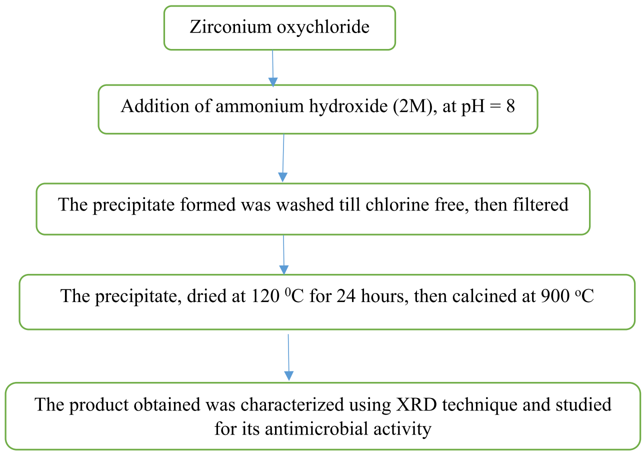

Figure 1. Scheme illustrating the preparation method of zirconia nanoparticles.

XRD analysis was performed to investigate the phase composition, and the Scherrer equation[34] was used for calculating the crystal size of the calcined ZrO_2 nanomaterial.

2.2. Microorganisms. *2.2.1. Microorganisms (Test: Bacteria).* Gram-positive bacteria *Staphylococcus aureus* ATCCBAA977 and *Streptococcus pneumoniae* ATCC49619 and Gram-negative bacteria *Escherichia coli* ATCC25922, *Salmonella typhimurium* ATCC14028, *Pseudomonas aeruginosa* ATCC27853, and *Alcaligenes aquatilis* were utilized as test organisms. All of the bacterial strains were acquired from the Microbiology Department, University of Jeddah. The bacteria were injected in a nutrient medium and kept at 37 °C for 48 h.

2.2.2. Microorganisms (Test: Fungi). Various fungal species, including *Aspergillus niger*, *Aspergillus flavus*, and *Penicillium* sp., were used as test organisms. All of the fungal strains were acquired from the Microbial from the Microbiology Department, University of Jeddah. The fungi isolates were cultivated for 7 days at 25 °C in a Sabouraud dextrose medium.[42]

2.3. Growth Medium. The Mueller−Hinton (MH) medium, which encourages microbial growth, was used for the preparation of bacteria and fungi. Agar well distribution is frequently used to evaluate the mobility of microbes that are resistant to antibiotics. The agar plate surface is immunized using a technique similar to the circle dissemination strategy, which involves spreading a volume of the microbial inoculum throughout the entire agar surface. At that time, a volume (10−20 mL) of the antimicrobial agent is delivered into the well by aseptically punching an aperture with a diameter of 2−4 mm using a sterile stopper borer or tip. Agar plates are then brooded under appropriate circumstances by using the test microorganism. The active agent in antimicrobials disperses in the agar medium and restrains the development of the microbial strain tried.[43]

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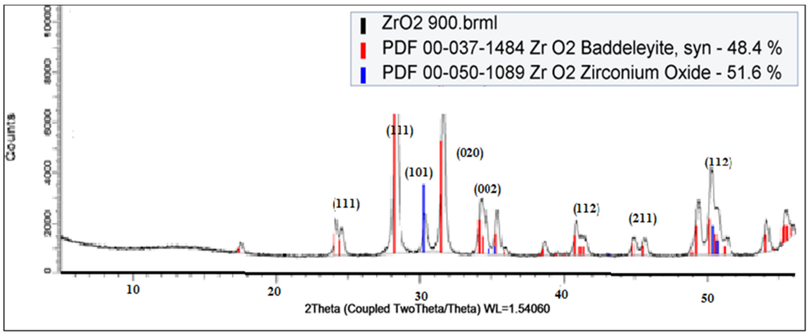

Figure 2. XRD patterns of the prepared powder.

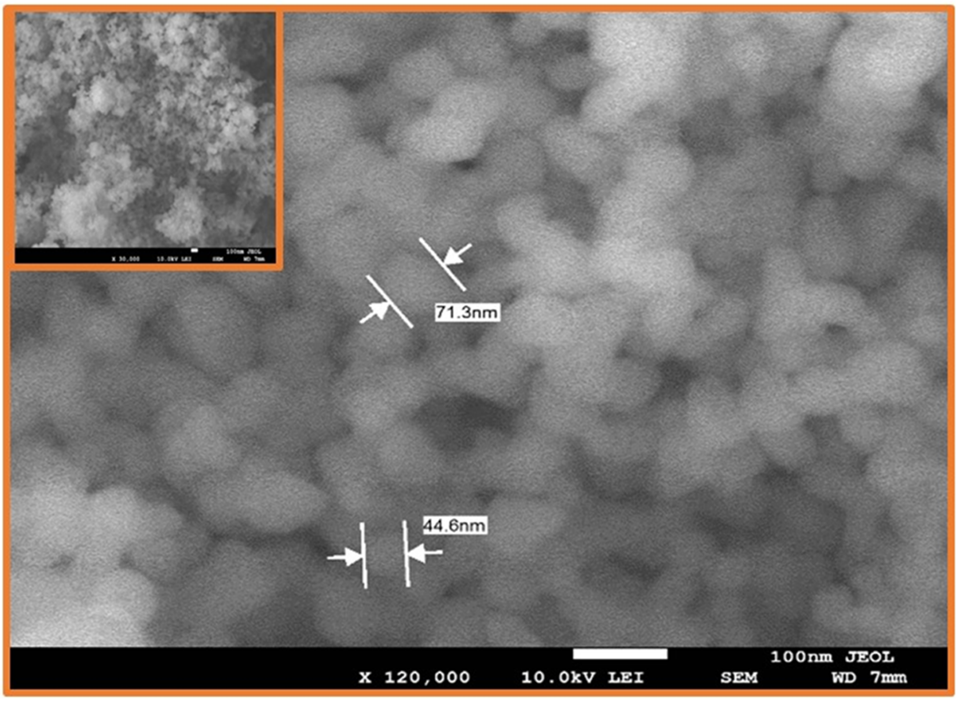

Figure 3. Scanning electron microscopy photomicrograph of the prepared nanozirconia powder.

2.4. Antimicrobial Test. Zirconium oxide nanomaterials were tested for in vitro antibacterial and antifungal activity by utilizing the agar-well diffusion method.[44] They were tested for their antibacterial activity against Gram-positive bacteria *S. aureus* ATCCBAA977 and *S. pneumoniae* ATCC49619 and Gram-negative bacteria *E. coli* ATCC25922, *S. Typhimurium* ATCC14028, *P. aeruginosa* ATCC27853, and *A. aquatilis* using the disk diffusion method. Zirconia nanoparticles were also tested for their antifungal efficacy against a variety of species, such as *Penicillium* sp., *A. niger*, and *A. flavus.* Using a sterile cotton swab and a sterile Petri plate containing the Mueller–Hinton agar medium, the bacterial inoculum concentration (6 × 10^6 CFU/mL) and fungal inoculum (4 × 10^5 CFU/mL) were uniformly dispersed. Zirconium oxide nanoparticles (2 mm in diameter) in MH agar medium were poured into the pores after agar disks (2 mm in diameter) were sliced off using a sterilized cork borer. Under aerobic conditions, the plates were incubated for 24 h at 37 °C. Bacterial growth that was confluent was seen after incubation. The growth in the bacterial and fungal inhibition zones was measured in millimeters. Average values were computed by following the completion of each trial in triplicate.

2.5. Procedure Solvents. A solution of water and dimethyl sulfoxide (DMSO) was prepared in different ratios ranging from 1 to 100% v/v of DMSO.[43] The incubation period was 24–48 h at 35 °C for bacterial growth, while for fungi, it was 7 days at 25 °C.

3. RESULTS AND DISCUSSION

3.1. Characterization of the Prepared ZrO_2 Nanoparticles. Figure 2 shows the XRD data for the prepared powder. It shows only two types of peaks indicating two different crystalline forms: zirconium oxide (JCPDS Card 00-037-1484) and Baddeleyite (JCPDS Card 00-037-1484). This reveals the high purity of ZrO_2, and by using the Scherrer equation from the XRD pattern, the crystal size was found to be in the range 40–75 nm, which proves that the ZrO_2 powder is in the nanoparticle form.

Indexing of all diffraction peaks shows two forms of ZrO_2 structures, i.e., tetragonal (51.6%) and monoclinic (48.4%) structures, but all diffraction peaks appear to be significantly sharp, indicating the purity and crystallinity of the prepared zirconium oxide.[51] They appear to be more sharp when the calcination temperature is increased.

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ACS Omega 2024, 9, 2945–2952

Figure 3 shows the scanning electron microscopy (SEM) image of the nanoparticle. It appears to have a round crystal shape from the photomicrograph, recognizing the ZrO_2 particles with diameter less than 100 nm as clearly seen from the figure, which confirms the phase of nano-ZrO_2 particles.

Figure 4, in which a table is inserted, shows the EDAX analysis of the prepared material with a round crystal shape that is composed of zirconium (69.33%) and oxygen (30.33%). The absence of any other elements indicates its purity.

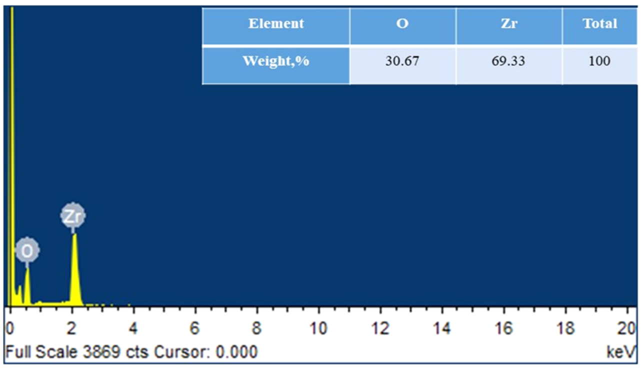

Figure 4. Elemental analysis chart (EDAX) of the prepared material.

3.2. Biological Activity of Nanozirconium Oxide (ZrO_2).

3.2.1. Antibacterial Activity of Nanozirconium Oxide. Nanozirconium oxide was tested for its antibacterial activity against Gram-positive bacteria, including *S. aureus* and *S. pneumoniae*, and Gram-negative bacteria, such as *E. coli, S. Typhimurium*, *P. aeruginosa*, and *A. aquatilis*. The bacterial strains were cultivated on both Mueller−Hinton (MH) agar and nutritional agar (OxioidCM41).

Gram-positive bacteria were used to test the effectiveness of the antimicrobial agent nanozirconium oxide, and the findings are presented in Figure 5. It was found that the concentration of the inhibitory effect enhances the inhibition effect against Gram-positive bacteria. *S. aureus* is more efficiently inhibited than *S. pneumoniae* by nanozirconium oxide at a 9% DMSO concentration, which is revealed by the size of the inhibitory zone. The diameter of the inhibitory zone of *S. aureus* is 3.50 mm, while that of *S. pneumoniae* is 3.40 mm at a 9% DMSO concentration.

Figure 5 shows how the microbial isolates exhibited resistance to Gram-positive bacteria-produced nanozirconium oxide. At a concentration of 3% DMSO, zirconium oxide nanoparticles were utilized to decrease the diameter of the inhibitory zone. The inhibitory zone had a diameter of 0.40 mm when used against *S. aureus* and a diameter of 0.50 mm when used against *St. pneumonia* at a dose of 3% DMSO.

Figure 6 shows the usage of Gram-negative bacteria to assess the antibacterial property of nanozirconium oxide. The findings show that the inhibition effect against Gram-negative bacteria increases when the inhibitory influence is concentrated. *Salmonella* spp. were severely inhibited by zirconium oxide nanoparticles due to the high sensitivity of the bacterium to them, as seen by the diameter of the inhibitory zone, which is 3.60 mm at a concentration of 9% DMSO. The diameter of the inhibitory zone when *A. aquatilis* and *P. aeruginosa* were suppressed revealed the microorganism's susceptibility to nanozirconium oxide. At a 9% DMSO concentration, their inhibitory zone is greater than that of *E. coli*, measuring 3.20 mm in diameter.

The microbial isolates, as depicted in Figure 6, were resistant to nanozirconium oxide, which was used to treat Gram-negative bacteria. In experiments with *S. Typhimurium, E. coli, P. aeruginosa*, and *A. aquatilis*, zirconium oxide nanoparticles of a concentration of 3% DMSO reduced the diameter of the inhibitory zone (0.004 mm).

Nano zirconia (ZrO_2) is a biologically active material primarily due to its unique physicochemical properties at the nanoscale. When zirconia particles are reduced to nanosize,

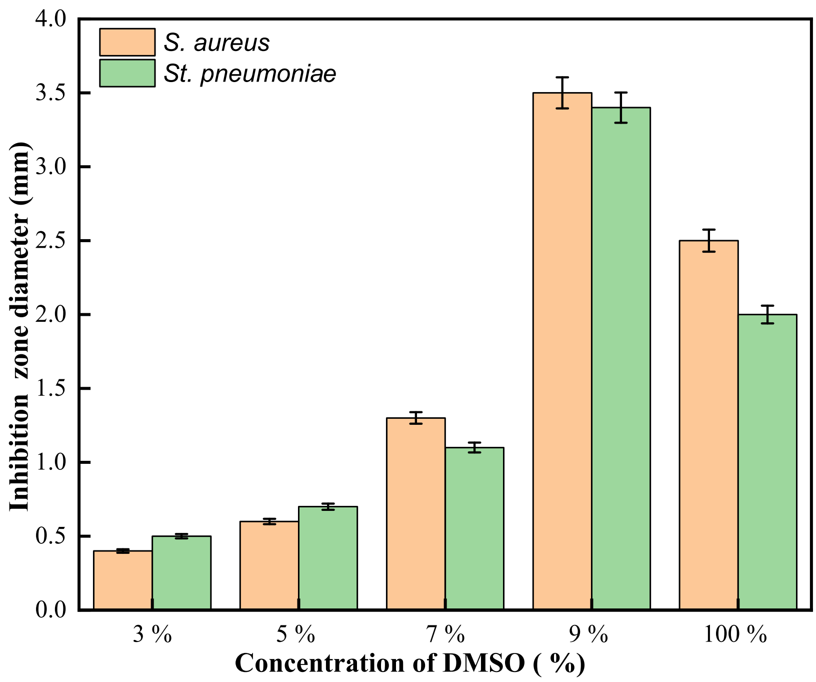

Figure 5. Measuring the halo of the antimicrobial activity of nanozirconium oxide against Gram-positive bacteria.

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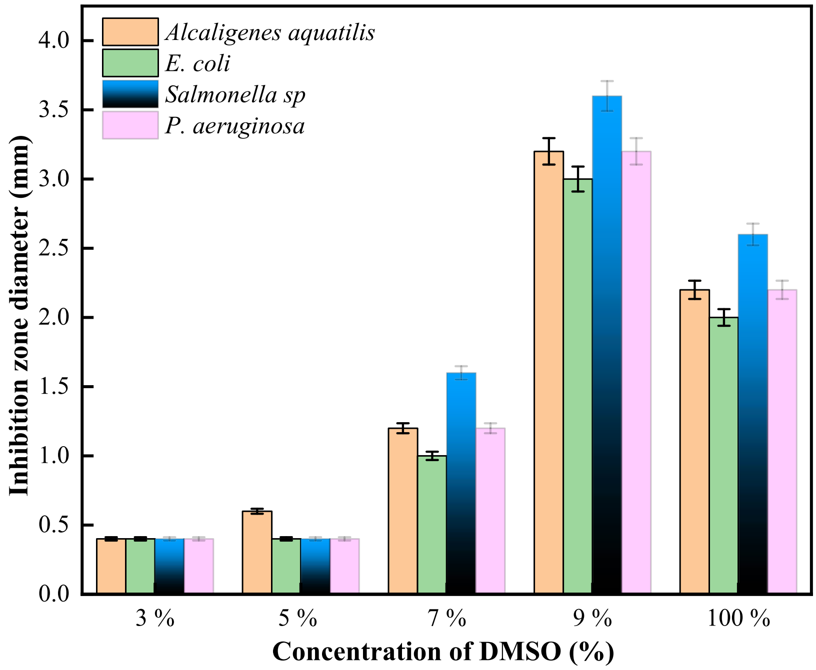

Figure 6. Measuring the halo of the antimicrobial activity of nanozirconium oxide against Gram-negative bacteria.

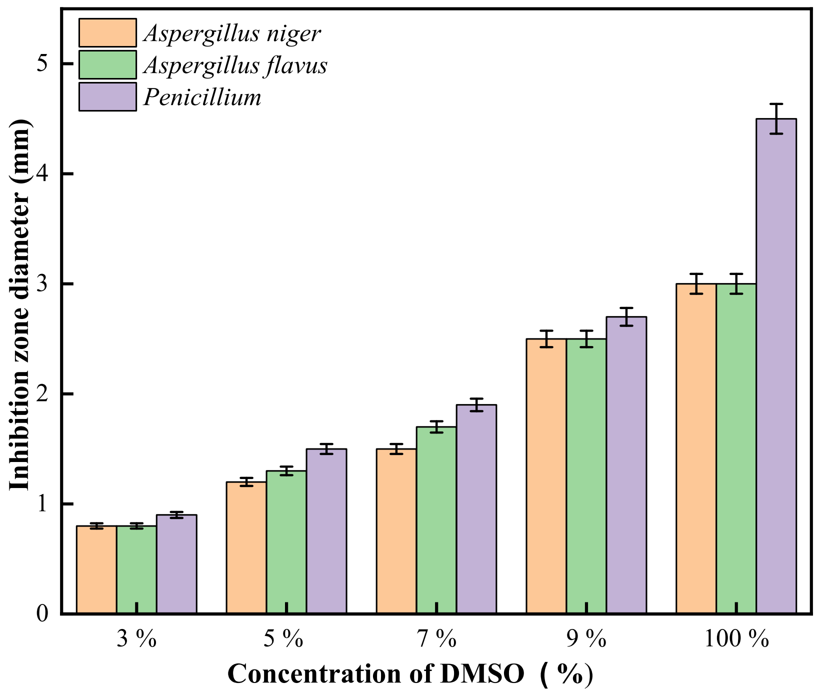

Figure 7. Measuring the halo of the antifungal activity of nanozirconium oxide.

they exhibit increased surface area, altered surface chemistry, and enhanced reactivity compared to their bulk counterparts. These properties make nano zirconia highly reactive and capable of interacting with biological systems.

The biological activity of nano zirconia can be attributed to several mechanisms. The increased surface area of nano zirconia allows for more interactions with surrounding molecules such as proteins, enzymes, and ions. This high surface reactivity enables nano zirconia to participate in various biological processes.[45] Nano zirconia can also release Zr^{4+} ions into its surrounding environment. These ions can interact with biological molecules and affect cellular processes. For example, Zr^{4+} ions can influence enzyme activity, gene expression, and cell signaling pathways.[46] Nano zirconia particles can induce oxidative stress in biological systems. Owing to their high reactivity, they can generate reactive oxygen species (ROS) when in contact with biological fluids or cellular components. ROS can lead to cellular damage and trigger inflammatory responses. Nano zirconia particles possess a surface charge that can interact with charged molecules, such as proteins and DNA. This interaction can affect the conformation, activity,

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ACS Omega 2024, 9, 2945−2952

and stability of these biomolecules, thereby influencing biological processes.[47]

3.2.2. Antifungal Activity of Nanozirconium Oxide. The antifungal activity of nanozirconium oxide, an antifungal agent, was tested, and the results are shown in Figure 7. The results show that the inhibition effect against the fungus was enhanced with the concentration of the inhibitory impact. The size of the inhibitory zone indicates how susceptible the bacterium is to nanozirconium oxide, which causes *Penicillium* to be more strongly inhibited at a 100% DMSO concentration. The diameter of the inhibitory zone is 4.50 mm in contrast to that of *A. niger* and *A. flavus* at a 100% DMSO concentration, which is 3.00 mm.

As can be seen in Figure 7, the microbial isolates demonstrated their resistance to fungal-produced nanozirconium oxide. Using *Penicillium* at a concentration of 3% DMSO, zirconium oxide nanoparticles reduced the diameter of the inhibitory zone. The inhibitory zone has a diameter of 0.80 mm.

In a study by Jangra Sant et al.,[48] the agar-well diffusion test method was used to evaluate the antibacterial activity of zirconium oxide (ZrO_2) nanomaterials against diverse bacterial and fungal species. Because the charge and chemical moieties of the outer membrane of Gram-positive bacteria (*S. aureus*) and Gram-negative bacteria (*E. coli*) differ significantly, it was found that the ZrO_2 nanoparticles showed antibacterial activity only against *E. coli* bacteria and no activity against *S. aureus* and fungus. According to a comparison of test compounds' antifungal activity data against different fungi, the compound is more effective against *B. cinerea* and *Aspergillus* than other fungi. Owing to the arrangement of the atoms, the bonds, and the surface energy, the shape of crystals can have a significant impact on how they respond chemically.[49] Surface energies differ between atomic planes.[50]

In a study by Ayodeji and Simon,[50] pure metal ZnO_2 nanoparticles' antibacterial action causes an increase in the production of reactive oxygen species (ROS), which in turn causes the bacterial cells to be destroyed. Lipid peroxidation is just one of the many impacts of these enhanced ROS on the bacteria. The integrity of the bacterial membrane is impacted by this lipid peroxidation. High levels of membrane leakage exist. The strength of the membrane is diminished. With increasing zinc oxide nanoparticle concentration, the bacterial cell wall is destroyed, which results in bacterial death. It depends on the amount of available surface area for interaction when ZnO_2 and Z−Z nanoparticles bind to bacteria. It is difficult to completely understand how nanoparticles penetrate materials. Nonetheless, it was revealed that the nanoparticles had the ability to penetrate bacteria, and this is dependent on the direct relationship between the size of the nanoparticle and the makeup of the bacterial membrane; treating bacteria with nanoparticles results in a fault in the cell membrane. The smaller the nanoparticles are, the higher the likelihood that they will breach the bacterial membrane, which results in their demise. Nanoparticles have helped pass the plasma membrane in the presence of ion channels and transporter proteins.

4. CONCLUSIONS

The as-prepared zirconium oxide (ZrO_2) nanomaterial was characterized using different techniques at 900 °C and subjected to antimicrobial assessment. The evaluation of ZrO_2 nanomaterials included various microbial strains. The antimicrobial activity of the prepared zirconium oxide nanomaterial was tested using a well diffusion method against different types of bacteria: Gram-negative bacteria such as *E. coli*, *S. paratyphi*, *P. aeruginosa*, and *A. aquatilis* and Gram-positive bacteria such as *S. aureus* and *S. pneumoniae*.

The antifungal activity of zirconium oxide nanoparticles was tested for *A. niger, A. flavus, and Penicillium* sp. The values of the diameter of the inhibitory zone reveal the degree of sensitivity of the microorganism. Thus, from the antimicrobial test results obtained from this work, zirconium oxide nanoparticles showed an effective resistance toward microbial growth.

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Notes

The authors declare no competing financial interest.

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