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ORIGINAL ARTICLE

Improved Study of Itraconzole's Effectiveness against *Candida parapsilosis*

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ABSTRACT

Objective: The present study aims to improvement efficiency of antifungal agent Itraconazole by nanotechnology.

Methods: Direct ion exchange between antibiotic itraconazole (ITZ) and zinc oxide layers (ZnO) was used to create a nanohybrid antibiotic ITZ-ZnO. FT-IR spectroscopy and X-Ray Diffraction were used to identify the novel nano antibiotic (XRD. The nanohybrid Itraconazole's antifungal efficacy was investigated against *Candida* isolate from urinary tract infections, that diagnosed by Vitek.

Results: The results showed that Fourier-transform infrared (FT-IR) spectroscopy results for the prepared antibiotics showed that the frequencies of some chemical groups shifted towards high and low frequencies. XRD revealed the presence of unique diffraction planes in the spectrum of the nanohybrid antibiotic when compared to the carrier spectrum Zinc oxide, which indicates that the prepared antibiotics under study is nanohybrid antibiotics.

The diagnosis of yeast by Vitek was *Candida parapsilosis*. The results of the statistical analysis showed that the diameter of inhibition increases significantly ($p \leq 0.05$) in the nanohyprid Itraconazole at a concentration of 100 µg/mL compared with the free Itraconazole, dimeters of inhibition zone at 100 µg/mL were (9.4 and 6.1) mm in nanoitraconazole and free Itraconazole, respectively.

Conclusions: The success of loading itraconazole on zinc oxide as a carrier of the antibiotic. The activity of the nano-hybrid compound of itraconazole and zinc oxide gave a higher inhibition activity compared to free itraconazole.

INTRODUCTION

Candidiasis is a yeast infection caused by *Candida albicans* (a type of fungus). *C. albicans*, the most common Candida species that may cause illness. Candida may survive on the skin and inside the body, in locations including the mouth, throat, gut, and vaginal canal, without creating difficulties. Candida can cause problems if it gets out of hand or goes body tissue (The bloodstream, for example, or internal organs like the kidney, heart, or brain).[1]

C. albicans is the most common cause of candidiasis, however other *Candida* species can also cause illness. *C. albicans* is a normal inhabitant which dwells in the vaginal canal and mouth, particularly on the dorsum of the tongue. *C. albicans* can also be found in moisture regions like skin creases. Infections typically emerge when the host's resistance or normal flora changes. Glucocorticoid medication, antibiotic therapy, especially wide or extended spectrum antibiotics, immunosuppressive and cytotoxic medicines, diabetes mellitus, nutritional inadequacies, other debilitating disorders, and xerostomia are all host factors that enhance the risk of candidiasis (dry mouth).

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Candidaiasis is also a risk in diseases characterized by immunodeficiency. In reality, the emergence of acquired immune deficiency illness (AIDS) has resulted in a large increase in candidiasis cases. Smokers and denture wearers are also more likely to acquire mouth cancer.[2]

C. parapsilosis is an important human pathogen that has drastically increased in importance and frequency over the last two decades, making it one of the most common causes of invasive candidal disease. Patients in intensive care unit (ICU) and newborns are at the highest risk of developing a deadly infection. Diseases with *C. parapsilosis* have been associated to hyperalimentation solutions, artificial limbs, and cannulation catheters, as well as clostridium difficile disease transmission through the hands of health-care workers. The production of hydrolytic enzymes, adherence to prostheses, and biofilm development are all factors in disease etiology. New molecular genetic methods are giving much-needed information on the pathogenicity of *C. parapsilosis*. The new information will help researchers better understand *C. parapsilosis* pathogenesis and aid in the development of new treatments for *C. parapsilosis* infections.[3]

Itraconazole is a triazole antibiotic that is used to treat fungus. Itraconazole may be used if a fungus or yeast is suspected of causing inflammatory skin disorders such as atopic eczema, seborrhoeic dermatitis, or psoriasis. Itraconazole has been found to slow the progression of basal cell carcinoma, and it is sometimes taken for this reason off-label. Itraconazole inhibits the production of ergosterol, a crucial component of the cell wall, by binding to the p450 enzymes prevalent in fungi. Itraconazole comes in 100 mg capsules and a 10 mg/mL liquid solution on prescription in New Zealand. Itraconazole, a generic, is occasionally funded. Janssen-Cilag owns the rights to the image. Itraconazole formulations are marketed under the name SporanoxTM. Sporanox oral liquid is covered by the Special Authority for children with immunodeficiency and associated infections.[4]

When given with something like a fatty diet or acidic fluid, the drug is absorbed rapidly directly. It binds to proteins in the blood, such as albumin, and concentrates in fat cells, as well as in the skin and nails. A total of 50% of the medicine is eliminated from the blood circulation in one to three days. The part is excreted in the feces and urine after the liver converts it to non-toxic compounds.[4]

The levels in the skin can be 3 to 10 times higher than that in the blood. It can stay in the skin for up to four weeks after the medicine is stopped, and it can stay in the nails for up to a year.[5]

This study aimed to overcome a resistance problem that produced by *Candida* sp. against antifungal agents which used in this study, and that is through the development of Itraconazole through the manufacture of a nano-hybrid compound from it.

MATERIALS AND METHODS

Preparation of Nanohybrid Itraconazole

The nanohybrid antibiotic was prepared using the process defined by Kolekar *et al*.[6]

Itraconazole Solution: This solution was prepared by dissolving 0.5 gm of the Itraconazole in an amount of 50% ethanol, and after completing the dissolution process, the volume was completed to 50 mL using ethanol.

Zinc Oxide Solution: This solution was prepared by dissolving 1-gm of the Zinc Oxide in an amount of 50% ethanol, and after completing the dissolution process, the volume was completed to 50 mL using ethanol as well.

Nanohybrid Itraconazole: Fifty mL of Itraconazole solution was added drop by drop to 50 mL Zinc oxid solution, and the combination was continuously stirred at ambient temperature for 2 hours before being put in a CO_2 incubator at 37°C for 18 hours and then a stable incubator at 40°C for 24 hours. The samples were centrifuged for 20 minutes at 5000 rpm, then washed three times with deionized water before being dried. ITZ-ZnO and ITZ-Free were assigned to the prepared nanohybrid antibiotic and free Itraconazole, respectively.

Characterization of the Nanohybrid Antibiotic

A number of techniques were used to investigate the generated nanohybrid antibiotic (ITZ-ZnO), such Fourier transform infrared spectroscopy (FT-IR), X-ray diffraction (XRD), atomic force microscopy (AFM), and others (SEM).

Specimens: *Candida* sp. was obtained from the University of Kerbala's Toxins Laboratory, Department of Clinical Laboratories, College of Applied Medical Sciences. Vitek identified this isolate.

Measurement of antimicrobial activity of Nanohybrid Itraconazole: ITZ-ZnO, ITZ-Free, were tested against *C. parapsilosis* using the agar well diffusion method defined by Egorove,[7] with antibiotic concentrations ranging from 25 to 100 µg/mL:

Activation of Candida: The yeast Candida sp. grown on PDA medium was activated by transferring a whole loop from a single isolated colony to 5 mL of Sabouraud broth medium and incubated at (35–37)ºC for 18 hours thereafter. It was diluted with distilled water of the diagnostic kit to obtain a turbidity equivalent to 3 MacFarland.

Antimicrobial Activity Assay: The inhibitory activity of the nanohybrid ITZaconazole was tested against *C. parapsilosis* yeast according to diffusion agar method[7] according to the following:

- The inoculum was diluted to obtain the equivalent of 0.5 MacFarland by comparing it to MacFarland.
- The inoculum was spread on a plate containing 20 mL of SDA well by swab (swab) and then left for an hour.
- Using a cork porrer with a diameter of 5 mm to make wells on the surface of the dishes, as the distance was equal between one hole and another.
- Graduated concentrations of nanohybrid Itraconazole as well as free Itraconazole ranging from (0, 25, 50, 75, 100 and 150) µg/mL were prepared by dissolving them in the distal water.
- Fifty microliters of each concentration of the nanohybrid Itraconazole under study were placed in each hole, and

incubated for one hour in the refrigerator, and then incubated in the incubator at 28°C for 24 hours.

- Fifty microliters of each concentration of the free ITZ were placed in each hole, and incubated for one hour in the refrigerator, and then incubated in the incubator at 28°C for 24 hours.
- The diameters of yeast growth inhibition (mm) were measured using a ruler after the incubation period was completed

Statistical Analysis

The Chi-square test and ANOVA one way test were used in the statistical analysis to find out if there are any significant differences between the variables explored in this study at $\alpha = 0.05$.[8]

RESULTS AND DISCUSSION

Characterization by using infrared spectrum FT-IR:

A. Infrared spectrum for free Itraconazole (ITZ): Figure 1 shows many of the unique bands of free Itraconazole appeared. The band at frequencies 3562.64 cm^{-1} indicate a stretch vibration of the hydroxyl group (O-H). The results also indicate the emergence of bands due to the C-H stretch vibration at the frequencies of (3389.04 and 3336.96) cm^{-1} . The appearance of the bands at frequency 2937.68 cm^{-1} , indicate to presence of aliphatic (C-H) stretch. As for the two bands appearing at the frequency (1460.16 and 1413.23) cm^{-1}, they return to the structural stretch of the benzene ring , C = C while the apparent band at frequency 1354.07 cm^{-1} returns to the C-N stretcher , while it is noticed that the C – F stretch of the two bonds between fluorine and carbon at the frequencies (1238.34 and 1122.61) cm^{-1}. When it is noticed that there are two bands at the frequencies (914.29 and 860.28) cm^{-1} due to the extra-plane bending of the aromatic C-H bonds.[9]

B. Infrared spectrum for Nanohybrid (ITZ-ZnO): As shown in Figure 2 observed from nanohybrid Itraconazole, FT-IR spectrum there is an overlap between the vibration of the broad carboxylic acid O-H stretch with the aromatic C-H band, as well as a noticeable shift towards a lower frequency, as the broadband appeared at the frequency 3448.84 cm^{-1}. The two bands appearing at the frequency 3134.43 cm^{-1} due to the C-H aliphatic stretch vibration had a significant. The strong band appeared at 1701.27 cm^{-1} due to the interference of the vibration of the stretch of the carbonyl group of carboxylic acid only suffered a slight shift towards a higher. The two bands, which appeared at (1550.82 and 1514.17) cm^{-1}, also suffered a shift towards a low and high frequency, respectively, and they are due to the structural stretching of the benzene ring. In addition to the above, it is clear from the figure that a new band appeared at 1456.30 cm^{-1} also related to the structural stretching of the benzene ring. The results also showed the presence of a stretch of the CN bond , which appeared at 1384.94 cm^{-1} and it suffered a slight shift towards a higher frequency. The process was also accompanied by the emergence of a new band at 1332.86 cm^{-1}, also returning to the stretching of the C -N group. At the frequency 1228.70 cm^{-1}, a strong band is observed that returns to the stretch of the C-F and has suffered a noticeable shift towards a lower frequency after it was at the frequency 1182.40 cm^{-1}. Finally, the two bands appearing at frequencies (947.08 and 825.56) cm^{-1} are due to the extra-plane bending of the aromatic C-H bonds.[9]

C- FT-IR Spectrum of Zinc Oxide: As illustrated in Figure 3, the FT-IR spectra of Zinc oxide revealed indistinct bands at 400 to 500 cm^{-1}, which were attributable to the metal bond Zn-O resonance.[10]

Characterization by using X-ray Diffraction Spectrum (XRD): Through using XRD spectrum of zinc oxide (carrier) and the nanohybrid antibiotic, the difference in the thickness of the ZnO layers before and after the intercalation of Itraconazole between ZnO layers was examined (ITZ - ZnO). In the spectrum of ZnO, Figure 4 shows the presence of three crystallographic planes (100, 002 and 101). With a crystalline distance of 0.281 nm, the first plane appeared at 31.29°. The plane (002) appears at 34.82 degrees with a crystalline distance of 0.259 nanometers, while the plane (101) appears at 36.29 degrees with a crystalline distance of 0.247 nanometers.[10] The XRD spectrum of ITZ-ZnO was shown in Figure 5, and the results confirmed that itraconazole was intercalated between

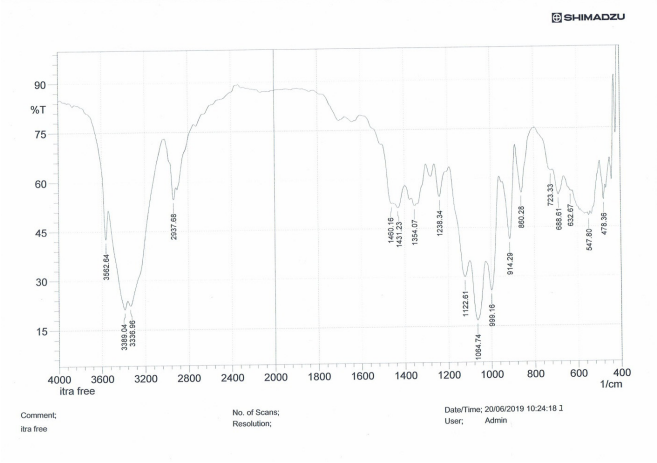

Figure 1: Infrared spectrum for ITZ-free

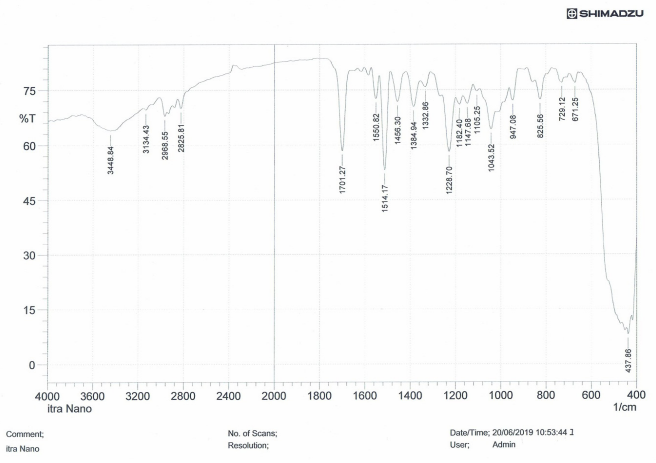

Figure 2: Infrared spectrum for ITZ-ZnO

ZnO layers. Two diffraction planes with crystalline distances of 0.68 and 0.24 nm appeared at 8.63° and 19.37°, respectively .

Precise Analysis of Elements in the Nanohybrid Itraconazole: Chemical analysis of the elements revealed that the percentages of carbon, nitrogen, and chloride were 30.57, 7.26 and 8.38% for ITZ-ZnO (Table 1).

Diagnosis of *Candida* sp.: The results of Candida diagnosis by Vitek through biochemical tests show that this isolated was *Candida parapsilosis* , as show in Table 2.

C. parapsilosis was previously divided into three groups: I, II, and III. Additional genetic studies, however, showed significant differences to divide the groupings into two distinct but related species: *C. parapsilosis*, *Candida orthopsilosis*, and *Candida metapsilosis* are all types of Candida.[11] Unfortunately, *C. parapsilosis* is associated for the most proportion of clinical illness, Few medical microbiology labs can tell the difference between these species, especially since commercial units aren't equipped to do so. Furthermore, few studies in the field have made this distinction; nevertheless, fresh criticisms are likely to consider the species separately.

C. parapsilosis is usually found on human skin as an intimate, and its toxicity is controlled by undamaged integument. *C. parapsilosis* is well-known for its capacity to expand in total parenteral nutrition (TPN) and form biofilms on catheters and other medical implants, as well as for nosocomial transmission via hand transport and permanence in the

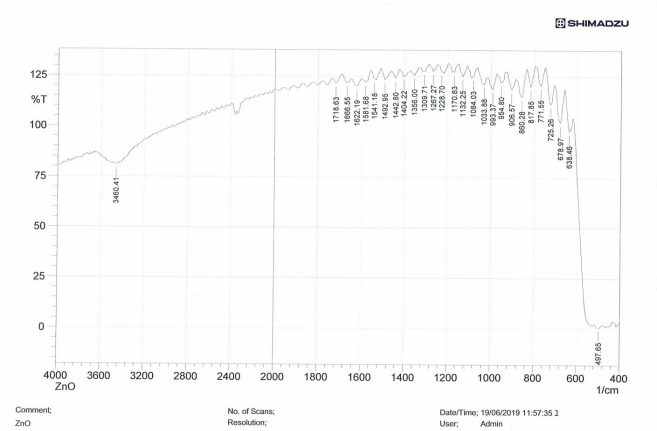

Figure 3: Infrared spectrum for zinc oxide

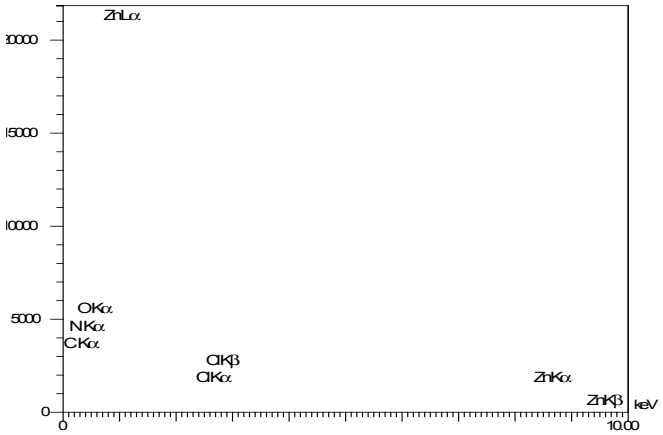

Figure 4: X-ray diffraction spectrum (XRD) for nano hybrid ITZaconazole

Table 1: C, N and Cl analysis of ITZaconazole

Elt	*Line*	*Int*	*Error*	*K*	*Kr*	*W%*	*A%*	*ZAF*	*Pk/Bg*	*LConf*	*HConf*
C	Ka	288.3	51.3459	0.1768	0.0675	30.57	44.02	0.2208	487.41	29.91	31.23
N	Ka	49.1	51.3459	0.0304	0.0116	7.26	8.97	0.1596	71.39	6.88	7.64
O	Ka	375.6	51.3459	0.2340	0.0894	35.00	37.85	0.2553	393.99	34.34	35.66
Cl	Ka	272.9	74.1938	0.1933	0.0738	8.83	4.31	0.8358	16.55	8.63	9.02
Zn	Ka	384.0	0.7834	0.3656	0.1396	18.34	4.85	0.7613	20.47	17.99	18.68
				1.0000	0.3819	100.00	100.00				

Table 2: Diagnostic results of biochemical tests for *Candida parapsilosis*

Test	*Result*	*Test*	*Result*	*Test*	*Result*	*Test*	*Result*
LysA	_	XLTa	_	ARG	+	dMLZa	+
TyrA	_	dTREa	+	AMYa	_	URE	_
dGLUa	+	dXYLa	+	dCELa	_	dGATa	+
dRAFa	_	2KGa	+	dMELa	_	CITa	+
IRHAa	_	LeuA	+	SACa	+	GLYLa	+
dTURa	+	ARBa	_	IARAa	+	GENa	_
IGLTa	+	MAdGa	+	ACEa	+	dMALa	+
IPROa	+	dMNEa	+	dGNTa	+	ISBEa	+
IMLTa	_	dSORa	+	ERYa	_	AGLU	+
BNAG	_	NO3a	_	dGALa	+	ESC	_
LACa	_	LATa	_	GGT	_	GRTas	+
NAGA1	_	NAGa	+				

healthcare setting.[12] *C. parapsilosis* is particularly harmful in critically ill infants, accounting for more than a quarter of all invasive fungal infections in low-birth-weight newborns in the United Kingdom[13] and up to one-third of neonatal Candida bloodstream infections in North America.[14] It's also the most prevalent fungus found in neonatal intensive care units (NICUs), where it's commonly associated to newborn deaths.[12,15,16]

Antimicrobial Activity

The results of the statistical analysis in Table 3 showed that there was a high significant difference ($p \leq 0.05$) in the diameters of inhibition zone of the free Itraconazole against *C. parapsilosis* at the concentrations (0, 25, 50, 75, 100 and 150) µg/mL compared with the control, while these concentrations did not show any significant difference ($p \geq 0.05$) in the diameters of inhibition when compared with each other. The diameters of inhibition zone were (0, 5.6 , 5.9, 6.0, 6.1 and 6.7) mm, respectively.

The results of the statistical analysis in Table 3 showed that there was a high significant difference ($p \leq 0.05$) in the diameters of inhibition zone of the nanohybrid Itraconazole against *C. parapsilosis* at the concentrations (0, 25, 50, 75, 100 and 150) µg/mL compared with the control, also these concentrations did show high significant difference ($p \leq 0.05$) in the diameters of inhibition when compared with each other. The diameters of inhibition zone were (0, 4.4 , 6.6, 8.8, 9.4 and 9.9) mm, respectively.

If comparing the free Itraconazole and nanohyprid Itraconazole, the results of the statistical analysis showed that the diameter of inhibition increases significantly ($p \leq 0.05$) in the nanohyprid Itraconazole at a concentration of 75, 100 and 150 µg/mL compared with the free Itraconazole, dimeters of inhibition zone these concentrations were (8.8 and 6.0), (9.4 and 6.1), (9.9 and 6.7) mm in nanoitraconazole and free Itraconazole, respectively.

These results show improvement the efficiency of Itraconazole by using nanotechnology method.

When it comes to azoles, The minimum inhibitory concentration of *C. parapsilosis* isolates is frequently low (MIC). Although most *C. parapsilosis* isolates have low MICs against azoles, recent research has shown that azole-resistant Candida can cause invasive infections. Isolates of *C. parapsilosis*. According to the results in one study, 89% (n = 94) of Isolates of *C. parapsilosis* had a MIC of 1-g/mL, showing resistance to ITZ. In 3.8 percent of the isolates, multi-azole resistance was found. Furthermore, with MIC50 values of 0.5 and 1-g/mL, respectively, LUZU and LZN displayed the maximum efficacy. MIC values against ITZ were found to be high in the most of the isolates. This can be related to the long-term use of ITZ prophylaxis/therapy in candidiasis patients. As a result, deciding on an effective antifungal medicine is an important initial step in the treatment procedure.[17]

The susceptibility pattern of itraconazole was evaluated using in vitro and clinical data in light of the updated cut-off points. Itraconazole's in vitro experiments was compared to those of eight comparators against 119 Candida bloodstream isolates from 2015 to 2018. The most effective antifungals against *Candida parapsilosis* were itraconazole, posaconazole, and amphotericin B. Itraconazole, voriconazole, and posaconazole were all susceptible to 96.9, 78.1, and 93.8% of the 32 isolates of *C. parapsilosis* that were resistant to fluconazole, accordingly. Against *C. parapsilosis* and *C. glabrata*, itraconazole had a lower ratio of MFC to MIC than the other azoles. Itraconazole was found to be more effective than fluconazole at inhibiting C. parapsilosis growth over time. 73 critically sick patients who were resistant to antibiotics were given itraconazole (n = 28) or placebo (n = 45) intravenous experimental therapy. Case-control comparisons were made for severity, comorbidities, candidemia risk factors, antibiotics used, and days of antifungal treatment. Threshold candidemia was identified in 3.6% of itraconazole-treated patients and 32.1% of comparator-treated patients (p : 0.020); breakthrough candidemia caused by *C. parapsilosis* was observed in 3.6% and 28.6% of patients, respectively. Itraconazole maintains a useful susceptibility profile versus Candida isolates, notably *C. parapsilosis*, according to the findings. This improved profile may explain the therapeutic potential in the incidence of breakthrough candidemia and calls for additional research.[17]

Minimum inhibitory dosages were used to assess the antifungal effects of silver(I) complex and itraconazole against four different Candida species (*C. albicans, C. glabrata, C. parapsilosis,* and *C. krusei*) (MICs). Agitraco complex outperforms itraco in terms of antifungal activity, being 2.3- and 4.5-fold more effective against *C. albicans* and *C. glabrata*, respectively. [18]

Resistance of fungal pathogens to commonly used antifungal medicines is on the rise and has become a severe issue. Nanoscience, but in the other hand, has served as a powerful technique for creating and designing novel antimicrobial medications. Nano compounds have distinct MICs in regular and resistant strains, including alone and in concert with antifungal medications. Ag-NPs reduced yeast

Table 3: The inhibitory efficacy of Nanohyprid Itraconazole against *C. parapsilosis*

	Concentration (µg/mL)							
Type of antifungal	*O (Control)*	*25*	*50*	*75*	*100*	*150*	*p-value*	*LSD*
Itraconazole (Free)	0 ± 0.00	5.6 ± 0.54	5.9 ± 0.87	6.0 ± 0.23	6.1 ± 0.79	6.7 ± 0.52	0.0000*	1.22
Itraconazole (Nano)	0 ± 0.00	4.4 ± 1.07	6.6 ± 0.50	8.8 ± 0.63	9.4 ± 1.42	9.9 ± 1.13	0.0000*	1.68
p-value	0.1000	0.0084 *	0.0527	0.0221 *	0.0001 *	0.0001 *		

The numbers refer to mean ± Standard Deviation * refers to high significance differences ($P \leq 0.01$)

growth at doses as low as 2 g/mL (against FLCR1 and FLCR3) and 0.25 g/mL (against FLCR1) (against ITRR2 and AMBR2). This will require more in vitro and in vivo research.[19]

CONCLUSIONS

According to the findings of our present research, we can draw several conclusions, the most important of which are: The species of *Candida* diagnosed is *parabicellosis*. The success of loading itraconazole on zinc oxide as a carrier of the antibiotic. The activity of the nano-hybrid compound of itraconazole and zinc oxide gave a higher inhibition activity compared to free itraconazole.

RECOMMENDATIONS

The following research summarize the recommendations:

- Testing another series of concentrations of nanohybrid on the isolate under study.
- Examination of nanohybrid itroconazole and zinc oxide on other isolates of *Candida*.
- Loading itraconazole on other carriers by methods other than the method used in this study.
- Study of the release of itraconazole and the periods of release in different liquids in its acidity.

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